US010359425B2

(12) **United States Patent**
Gold et al.

(10) **Patent No.: US 10,359,425 B2**
(45) **Date of Patent: Jul. 23, 2019**

(54) **LUNG CANCER BIOMARKERS AND USES THEREOF**

(75) Inventors: **Larry Gold**, Boulder, CO (US); **Marty Stanton**, Boulder, CO (US); **Edward N. Brody**, Boulder, CO (US); **Rachel M. Ostroff**, Westminster, CO (US); **Dominic Zichi**, Boulder, CO (US); **Alex A. E. Stewart**, Waltham, MA (US)

(73) Assignee: **SomaLogic, Inc.**, Boulder, CO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 334 days.

(21) Appl. No.: **12/556,480**

(22) Filed: **Sep. 9, 2009**

(65) **Prior Publication Data**

US 2010/0070191 A1 Mar. 18, 2010

Related U.S. Application Data

(60) Provisional application No. 61/095,593, filed on Sep. 9, 2008, provisional application No. 61/152,837, filed on Feb. 16, 2009.

(51) **Int. Cl.**
G01N 33/574 (2006.01)

(52) **U.S. Cl.**
CPC ***G01N 33/57423*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,660,985	A	8/1997	Pieken et al.
6,004,267	A	12/1999	Tewari et al.
6,335,170	B1	1/2002	Orntoft et al.
6,631,330	B1	10/2003	Poynard
7,081,340	B2	7/2006	Baker et al.
7,090,983	B1	8/2006	Muramatsu et al.
7,189,507	B2	3/2007	Mack et al.
7,521,195	B1	4/2009	Joseloff et al.
7,526,387	B2	4/2009	Baker et al.
7,569,345	B2	8/2009	Cobleigh et al.
7,582,441	B1	9/2009	Ruben et al.
7,622,251	B2	11/2009	Baker et al.
7,695,913	B2	4/2010	Cowens et al.
7,723,033	B2	5/2010	Baker et al.
7,767,391	B2	8/2010	Scott et al.
7,807,392	B1	10/2010	Domon
7,838,224	B2	11/2010	Baker et al.
7,858,304	B2	12/2010	Baker et al.
7,862,995	B2	1/2011	Bacus et al.
7,871,769	B2	1/2011	Baker et al.
7,888,019	B2	2/2011	Kiefer et al.
7,892,760	B2	2/2011	Birse et al.
7,930,104	B2	4/2011	Baker et al.
7,939,261	B2	5/2011	Baker et al.
7,947,447	B2	5/2011	Zichi et al.
8,008,003	B2	8/2011	Baker et al.
8,014,957	B2	9/2011	Radich et al.
8,019,552	B2	9/2011	Dai et al.
8,026,060	B2	9/2011	Watson et al.
8,029,995	B2	10/2011	Watson et al.
8,034,565	B2	10/2011	Cobleigh et al.
8,067,178	B2	11/2011	Baker et al.
8,071,286	B2	12/2011	Baker et al.
8,450,069	B2	5/2013	Goix et al.
8,632,983	B2	1/2014	Haab et al.
2003/0215895	A1	11/2003	Wennerberg et al.
2004/0009489	A1	1/2004	Golub et al.
2004/0241653	A1	12/2004	Feinstein et al.
2005/0069963	A1	3/2005	Loskin et al.
2005/0095611	A1	5/2005	Chan et al.
2005/0181375	A1 *	8/2005	Aziz et al. 435/6
2005/0214826	A1	9/2005	Mor et al.
2005/0260639	A1	11/2005	Nakamura et al.
2005/0260697	A1	11/2005	Wang et al.
2006/0019256	A1	1/2006	Clarke et al.
2006/0223127	A1	10/2006	Yip et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CN	101283106 A	10/2008
CN	102084253 A	6/2011

(Continued)

OTHER PUBLICATIONS

Shen et al (Cancer Research, 2006, 66:11194-11206).*
Brody and Gold (Reviews in Molecular Biotechnology, 2000, 74:5-13).*
Lemos-Gonzalez et al (British Journal of Cancer, Apr. 2007, 96:1569-1578).*
Charalabopoulos et al (Exp Oncol, 2006, 28:83-85).*
Park et al (Chest, 2007, 132:200-206).*
Tas et al (Cancer Investigation, 2006, 24:576-580).*
Suzuki et al (Lung Cancer 2002, 35:29-34).*
Jager et al (British Journal of Cancer, 2002, 86:858-863).*
Saad et al (Cancer, 2008, 113:2129-2138, published online Aug. 20, 2008).*

(Continued)

Primary Examiner — Laura B Goddard
(74) *Attorney, Agent, or Firm* — Adsero IP

(57) **ABSTRACT**

The present application includes biomarkers, methods, devices, reagents, systems, and kits for the detection and diagnosis of lung cancer. In one aspect, the application provides biomarkers that can be used alone or in various combinations to diagnose lung cancer or permit the differential diagnosis of pulmonary nodules as benign or malignant. In another aspect, methods are provided for diagnosing lung cancer in an individual, where the methods include detecting, in a biological sample from an individual, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers provided in Table 1, Col. 2, wherein the individual is classified as having lung cancer, or the likelihood of the individual having lung cancer is determined, based on the at least one biomarker value.

9 Claims, 22 Drawing Sheets

(56) **References Cited**

U.S. PATENT DOCUMENTS

2007/0099209	A1	5/2007	Clarke et al.
2007/0105142	A1	5/2007	Wilhelm et al.
2007/0178108	A1	8/2007	Dillon et al.
2007/0178504	A1	8/2007	Colpitts et al.
2007/0212721	A1	9/2007	Fischer et al.
2008/0057590	A1	3/2008	Urdea et al.
2008/0090258	A1	4/2008	Lokshin
2008/0171319	A1	7/2008	Urdea et al.
2008/0305962	A1	12/2008	Wirtz et al.
2009/0005268	A1	1/2009	Berlin
2009/0023149	A1	1/2009	Knudsen et al.
2009/0042229	A1	2/2009	Folkman et al.
2009/0053189	A1	2/2009	Glimcher et al.
2009/0104617	A1	4/2009	Gordon et al.
2009/0176228	A1	7/2009	Birse et al.
2009/0233286	A1	9/2009	Segara et al.
2010/0086948	A1	4/2010	Gold et al.
2010/0184034	A1	7/2010	Bankaitis-Davis et al.
2010/0221752	A2	9/2010	Gold et al.
2010/0267041	A1	10/2010	Shuber et al.
2010/0279419	A1	11/2010	Streckfus et al.
2011/0003707	A1	1/2011	Goix et al.
2011/0059103	A1	1/2011	Briessen et al.
2011/0144914	A1	6/2011	Harrington et al.
2011/0236903	A1	9/2011	McClelland et al.
2012/0077695	A1	3/2012	Ostroff et al.
2012/0101002	A1	4/2012	Riel-Mehan et al.
2012/0143805	A1	6/2012	Gold et al.
2012/0165217	A1	6/2012	Gold et al.
2013/0085079	A1	4/2013	Gill et al.
2013/0116150	A1	5/2013	Wilcox et al.
2014/0073521	A1	3/2014	Ostroff et al.
2014/0073522	A1	3/2014	Williams et al.
2015/0168423	A1	6/2015	Gill et al.
2018/0045739	A1	2/2018	Williams et al.
2018/0275143	A1	9/2018	Wilcox et al.

FOREIGN PATENT DOCUMENTS

CN	102209968	A	10/2011
GB	2478441		3/2013
JP	2005-527180	A	9/2005
JP	2006-53113	A	2/2006
RU	2376372		12/2009
WO	WO 2002/073204		9/2002
WO	WO 2002/086443		10/2002
WO	WO 2004/031412		4/2004
WO	WO 2004/074510		9/2004
WO	WO 2004/075713		9/2004
WO	WO 2004/099432		11/2004
WO	WO 2005/043163		5/2005
WO	WO 2005/083446		9/2005
WO	WO 2005/103281		11/2005
WO	WO 2006/022895		3/2006
WO	WO 2006/063213		6/2006
WO	WO 2007/013665	A1	2/2007
WO	WO 2007/045996	A1	4/2007
WO	WO 2007/109571		9/2007
WO	WO 2008/046911	A1	4/2008
WO	WO 2008/063413	A2	5/2008
WO	WO 2008/117067	A9	10/2008
WO	WO 2009/036123		3/2009
WO	WO 2009/091581		7/2009
WO	WO 2009/103542	A1	8/2009
WO	WO 2010/028658	A1	3/2010
WO	WO 2010/142713		12/2010
WO	WO 2011/059721		5/2011
WO	WO 2011/068839		6/2011
WO	WO 2011/072177		6/2011
WO	WO 2011/094483		8/2011
WO	WO 2013/142114		9/2013

OTHER PUBLICATIONS

Fuji et al (Journal of Proteome Research, 2004, 3:712-718).*
Bock et al (Proteomics, 2004, 4:609-618).*
McCauley et al (Analytical Biochemistry, 2003, 319:244-250).*
Brody et al (Reviews in Molecular Biotechnology, 2000, 74:5-13).*
Burgess et al (Proteomics Clinical Application, Jul. 30, 2008, 2:1223-1233).*
Mikolajczyk et al (Clinical Biochemistry, 2004, 37:519-528).*
Miller et al (Proteomics, 2003, 3:56-63).*
HUGO Gene Nomenclature Committee, Symbol Report for "CNDP1" printed May 2015.*
HUGO Gene Nomenclature Committee, Symbol Report for "MMP7" printed May 2015.*
Great Britain Examination Report dated Sep. 20, 2011 in GB 1106053.0.
International Search Report and Written Opinion dated May 18, 2010 in PCT/US2010/0029878.
International Search Report and Written Opinion dated Apr. 30, 2010 in PCT/US2010/026439.
Bock et al. (Mar. 1, 2004) Proteomics 4(3):609-618 "Photoaptamer arrays applied to multiplexed proteomic analysis".
European Search Report dated May 7, 2012 in EP 09819761.9.
Gray et al. (2009) J Thorac Oncoll 4(3):411-425, "In arrayed ranks: array technology in the study of mesothelioma".
Great Britain Search Report dated Feb. 7, 2012 in GB 1106053.0.
Great Britain Examination Report dated Feb. 7, 2012 in GB 1106053.0.
Hoffmann (2005) Clin Cancer Res 11(3):1086-1092, "Matrix metalloproteinase-13 expression correlates with local recurrence and metastic disease in non-small cell lung cancer patients".
International Search Report and Written Opinion dated Feb. 28, 2012 in PCT/US2011/057499.
Mohr et al. (2004) Biochim Biophys Acta. 1688(1):43-60, "Cell protection, resistance and invasiveness of two malignant mesotheliomas as assessed by 10K-microarray".
European Search Report dated Jan. 17, 2012 in EP 09813557.7.
Amonkar et al. (Feb. 2009) PLoS. One, 4(2):e4599, "Development and preliminary evaluation of a multivariate index assay for ovarian cancer".
Baron et al. (Feb. 1999) Cancer Epidemiology; Biomarkers & Prevention 8:129-137, "Serum sErB1 and Epidermal Growth Factor Levels as Tumor Biomarkers in Women with Stage III or IV Epithelial Ovarian Cancer".
Bignotti et al. (2006) Gynecol. Oncol., 103:405-416, "Differential gene expression profiles between tumor biopsies and short-term primary cultures of ovarian serous carcinomas: Identification of novel molecular biomarkers for early diagnosis and therapy".
Chen, et al. (2008) Proteome. Sci. 6:20; pp. 1-11, "Profiling of serum and tissue high abundance acute-phase proteins of patients with epithelial and germ line ovarian carcinoma".
Diamandis, et al. (2000) Clin. Biochem. 33(7):579-583, "Human Kallikrein 6 (Zyme/Protease M/Neurosin): A new serum biomarker of ovarian carcinoma".
Erdogan et al. (2007) APMIS, 115, 204-209, "C-kit protein expression in uterine and ovarian mesenchymal tumours".
Gortzak-Uzan et al. (2008) J. Proteome. Res., 7:339-351, "A proteome resource of ovarian cancer ascites: integrated proteomic and bioinformatic analyses to identify putative biomarkers".
Granville et al. (2005) Am. J. Respir. Cell. Mol. Biol. 32:169-176, "An Overview of Lung Cancer Genomics and Proteomics".
Havrilesky et al. (2008) Gynecol. Oncol. 110:374-382, "Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence".
Heo et al. (2007) Proteomics. 7(23):4292-4302, "Identification of putative serum glycoprotein biomarkers for human lung adenocarcinoma by multilectin affinity chromatography and LC-MS/MS".
Jäger et al. (2002) British Journal of Cancer 86:858-863, "Serum levels of the angiogenic factor pleiotrophin in relation to disease stage in lung cancer patients".
Kim et al. (2006) J. Korean Med. Sci., 21:81-85, "Expression and mutational analysis of c-kit in ovarian surface epithelial tumors".
Kioi et al. (Sep. 2006) Cancer 107(6):1407-1418, "Interleukin-13 receptor alpha2 chain: A potential biomarker and molecular target for ovarian cancer therapy".

(56) **References Cited**

OTHER PUBLICATIONS

Kuk et al. (2009) Mol. Cell Proteomics 8:661-669, "Mining the ovarian cancer ascites proteome for potential ovarian cancer biomarkers".

Lassus et al. (2004) Br. J. Cancer, 91:2048-2055, "Genetic alterations and protein expression of KIT and PDGFRA in serous ovarian carcinoma".

Maciel et al. (2005) J. Exp. Ther. Oncol. 5:31-38, "Differential proteomic serum pattern of low molecular weight proteins expressed by adenocarcinoma lung cancer patients".

Moore et al. (2008) Gynecol. Oncol.108:402-408, "The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass".

Mor et al. (May 24, 2005) PNAS 102(21):7677-7682, "Serum protein markers for early detection of ovarian cancer".

Nolen et al. (Jan. 2009) Gynecol. Oncol.112(1):47-54, "A serum based analysis of ovarian epithelial tumorigenesis".

Ogata et al. (2006) J. Proteome. Res. 5:3318-3325, "Elevated levels of phosphorylated fibrinogen-alpha-isoforms and differential expression of other post-translationally modified proteins in the plasma of ovarian cancer patients".

Olchovsky et al. (2002) Acta Oncologica 41(2):182-187, "Elevated Insulin-Like Growth Factor-1 and Insulin-Line Growth Factor Binding Protein-2 in Malignant Pleural Effusion".

Palmer et al. (Jul. 2008) PLoS. One., 3(7):e2633, "Systematic evaluation of candidate blood markers for detecting ovarian cancer".

Park et al. (2008) Journal of Proteome Research 7:1138-1150, "Proteomic Profiling of Endothelial Cells in Human Lung Cancer".

Patz et al. (Dec. 10, 2007) Journal of Clinical Oncology, 25(35):5578-5583, "Panel of Serum Biomarkers for the Diagnosis of Lung Cancer".

PCT Search Report and Written Opinion dated Nov. 20, 2009 in PCT/US2009/056399.

PCT IPRP dated Sep. 30, 2010 in PCT/US2009/056399.

Planque et al. (Mar. 1, 2008) Clin. Cancer Res. 14(5):1355-1362, "A Multiparametric Serum Kallikrein Panel for Diagnosis of Non-Small Cell Lung Carcinoma".

Polanski et al. (2006) Biomark. Insights. 1-48, "A list of candidate cancer biomarkers for targeted proteomics".

Polanski et al. (2006) Biomark. Insights (Supplement).

Pouniotis et al. (2005) British Society for Immunology, Clinical and Experimental Immunology 143:363-372, "Alveolar macrophage function is altered in patients with lung cancer".

Ranshoff (Feb. 16, 2005) Journal of the National Cancer Institute 97(4):315-319, "Lessons from Controversy: Ovarian Cancer Screening and Serum Proteomics".

Rosen et al. (2005) Gynecol. Oncol. 99:267-277, "Potential markers that complement expression of CA125 in epithelial ovarian cancer".

Salam et al. (2009) Med. Oncol. 26:161-166, "Serum levels of epidermal growth factor and HER-2 neu in non small-cell lung cancer: prognostic correlation".

Shih et al. (2007) Gynecol. Oncol. 105:501-507, "Ovarian cancer specific kallikrein profile in effusions".

Suzuki et al. (2002) Lung Cancer 35(1): 29-34, "Serum endostatin correlates with progression and prognosis of non-small cell lung cancer".

Swidzińska et al. (2005) Rocz. Akad. Med. Bialymst 50:197-2000, "Serum endostatin levels in patients with lung carcinoma" (abstract only).

Tamura et al. (2002) The International Journal of Biological Markers 17(4):275-279, "Diagnostic value of plasma vascular endothelial growth factor as a tumor marker in patients with non-small cell lung cancer".

Tchagang et al. (Jan. 2008) Mol. Cancer Ther. 7(1):27-37, "Early detection of ovarian cancer using group biomarkers".

Tonary et al. (2000) Int. J. Cancer, 89:242-250, "Lack of expression of c-Kit in ovarian cancers is associated with poor prognosis".

Tsukishiro et al. (2005) Gynecol. Oncol. 96:516-519, "Use of serum secretory leukocyte protease inhibitor levels in patients to improve specificity of ovarian cancer diagnosis".

Welsh et al. (Mar. 2003) PNAS 100(6):3410-3415, "Large-scale delineation of secreted protein biomarkers overexpressed in cancer tissue and serum".

Zhonghua (Jul. 18, 2006) Yi Xue Za Zhi. 86(27):1916-18, "The value of serum endostatin level in early diagnosis of lung cancer" (abstract only).

Office Action dated Jun. 24, 2011 in U.S. Appl. No. 12/574,341.

Greenbaum (Sep. 1, 2001) Genome Research, Cold Spring Harbor Laboratory 11(9):1463-1468, "Interrelating different types of genomic data, from proteome to secretome: 'Oming in on function'".

Great Britain Examination Report dated Jan. 10, 2013 in GB 1106053.0.

International Preliminary Report on Patentability dated Jan. 15, 2013 PCT/US2011/043595.

Chen et al. (2008) Chem Med Chem 3:991-1001, "Molecular Recognition of Small-Cell Lung Cancer Cells Using Aptamers".

Kettunen et al. (2004) Cancer Genetics and Cytogenetics 149:98-106 "Differentially expressed genes in nonsmall cell lung cancer: expression profiling of cancer-related genes in squamous cell lung cancer".

ADAPT website by the Patterson Institute for Cancer Research, pro besets for MMP7, printed May 22, 2013.

ADAPT website by the Patterson Institute for Cancer Research, probesets for Cadherin-5 (CDH5), printed May 22, 2013.

ADAPT website by the Patterson Institute for Cancer Research, probesets for ERBB1 (EGFR), printed May 22, 2013.

Borrebaeck (2006) Expert Opin. Biol. Ther. 6(8):833-838 "Antibody microarray-based oncoproteomics".

Chen et al. (2002) Molecular and Cellular Proteomics 1:304-323 "Discordant Protein and mRNA Expression in Lung Adenocarcinomas*".

Gao et al. (Aug. 2005) BMC Cancer 5:110 (internet pp. 1-10) "Distinctive serum protein profiles involving abundant proteins in lung cancer patients based upon antibody microarray analysis".

Honda et al. (2013) Jpn J Clin Oncol 43(2)103-109, "Proteomic Approaches to the Discovery of Cancer Biomarkers for Early Detection and Personalized Medicine".

Kojima et al. (2008) J Gastrointest Surg 12:1683-1690, "Applying Proteomic-Based Biomarker Tools for the Accurate Diagnosis of Pancreatic Cancer".

Li et al (2006) Journal of Clinical Oncology, 24:1754-1760, "Serum Circulating Human mRNA Profiling and Its Utility for Oral Cancer Detection".

European Search Report dated Dec. 4, 2013 in EP 11804482.5.

Mercer (1990) Immunol. Ser., 1990;53:39-54, "Use of Multiple Markers to Enhance Clinical Utility".

Hoffman (2006) Oncology Reports 16(3):587-595, "Identification and classification of differentially expressed genes in non-small cell lung, cancer by expression profiling on a global human 59.620 element oligonucleotide array".

Ostroff et al., (2010)Journal of Proteomics,, pp. 649-666, "The stability of the circulating human proteome to variations in sample collection and handling procedures measured with an aptamer-based proteomics array".

Stearman et al., (2008) Cancer Research, 68(1):34-43, "A Macrophage Gene Expression Signature Defines a Field Effect in the Lung Tumor Microenvironment".

Thakur et al. (Jan. 24, 2008) Mol Cancer 7:11, "Gene expression profiles in primary pancreatic tumors and metastatic lesions of Ela-c-myc transgenic mice" doi:10.1186/1476-4598-7-11.

Zhong et al. (2003) Cancer Detection and Prevention 27:285-290, "Antibodies to HSP70 and HSP90 in serum in non-small cell lung cancer patients".

ADAPT website, The Paterson Institute for Cancer Research, probesets for EGFR, printed Jan. 29, 2014.

ADAPT website, The Paterson Institute for Cancer Research, probesets for CDH1, printed Jan. 29, 2014.

ADAPT website, The Paterson Institute for Cancer Research, probesets for VEGF, printed Jan. 29, 2014.

(56) **References Cited**

OTHER PUBLICATIONS

Hongsachart (2009) Electrophoresis 30:1206-1220, "Glycoproteomic analysis of WGA-bound glycoprotein biomarkers in sera from patents with lung adenocarcinoma".
International Preliminary Report on Patentability dated Apr. 29, 2014 in PCT/US2011/057499.
Spira et al (Mar. 2007) "Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer" Nature Medicine, 13(3):361-366.
Herszényl et al. (2008) European Journal of Cancer Prevention 17(5):438-445 "Serum cathepsin B and plasma urokinase-type plasminogen activator levels in gastrointestinal tract cancers".
Leto et al. (1997) Pancreas 14(1):22-27 "Lysosomal aspartic and cysteine proteinases serum levels in patients with pancreatic cancer or pancreatitis".
Tumminello et al. (1996) Int'l Institute of Anticancer Research 16(4B):2315-2319 "Cathepsin D, B and L circulating levels as prognostic markers of malignant progression".
Chang et al. (2009) Journal of Translational Medicine, 7(1):105, "Identification of a biomarker panel using a multiplex proximity ligation assay improves accuracy of pancreatic cancer diagnosis".
Yaziji et al. (2006) Modern pathology 19(4):514-523, "Evaluation of 12 antibodies for distinguishing epithelioid mesothelioma from adenocarcinoma: identification of a three-antibody immunohistochemical panel with maximal sensitivity and specificity".
Aspinall-O'Dea et al. (2007) Proteomics Clin. Appl. 1:1066-1079 "The pancreatic cancer proteome—recent advances and future promise".
Chen et al. (2005) Gastroenterology 129:1187-1197 "Pancreatic Cancer Proteome: The Proteins That Underlie Invasion, Metastasis, and Immunologic Escape".
Dowling et al. (2007) Electrophoresis 28(23):4302-4310 "2D difference gel electrophoresis of the lung squamous cell carcinoma versus normal sera demonstrates consistent alterations in the levels of ten specific proteins".
Ehmann et al. (2007) Pancreas 34:205-214 "Identification of Potential Markers for the Detection of Pancreatic Cancer Through Comparative Serum Protein Expression Profiling".
European Search Report dated Apr. 7, 2014 in EP 11874668.4.
Grønborg et al. (2004) Journal of Proteome Research 3:1042-1055 "Comprehensive Proteomic Analysis of Human Pancreatic Juice".
Ingvarsson et al. (2008) Proteomics 8:2211-2219 "Detection of pancreatic cancer using antibody microarray-based serum protein profiling".
Kearse et al. (2000) Int. Journal of Cancer 88:866-872, "Monoclonal AntiBody DS6 Detects A Tumor-Associated Sialoglycotope Expressed On Human Serous Ovarian Carcinomas".
Kuhlmann et al. (2007) Cancer Epidemiol Biomarkers Prey 16(5):886-91 "Evaluation of Matrix Metalloproteinase 7 in Plasma and Pancreatic Juice as a Biomarker for Pancreatic Cancer".
Louhimo et al. (2004) Oncology 66:126-131 "Serum HCGβ and CA 72-4 Are Stronger Prognostic Factors than CEA, CA 19-9 and CA 242 in Pancreatic Canter".
Lowe et al. (2007) PLoS ONE 2(3):e323 "Gene Expression Patterns in Pancreatic Tumors, Cells and Tissues".
Niedergethmann et al. (2004) Pancreas 29(3):204-211 "Prognostic Impact of Cysteine Proteases Cathepsin B and Cathepsin L in Pancreatic Adenocarcinoma".
Ohta et al. (1994) Br. J. Cancer, 69:152-156 "Pancreatic trypsinogen and cathepsin B in human pancreatic carcinomas and associated metastatic lesions".
Ohta et al. (1995) Gallbladder and Pancreas 16(5):407-412 "Mechanism and Control of Metastasis of Pancreatic Cancer—New Discovery".
Okada et al. (2006) Clin Cancer Res 12(1): 191-197 "A Novel Cancer Testis Antigen That Is Frequently Expressed in Pancreatic, Lung, and Endometrial Cancers".
Orchekowski (2005) Cancer Res 65(23):11193-11202 "Antibody Microarray Profiling Reveals Individual and Combined Serum Proteins Associated with Pancreatic Cancer".
Orchekowski (2005) Cancer Res 65(23) Supplemental "Antibody Microarray Profiling Reveals Individual and Combined Serum Proteins Associated with Pancreatic Cancer".
Rosty et al. (2002) Cancer Research 62:1868-1875 "Identification of Hepatocarcinoma-Intestine-Pancreas/Pancreatitis-associated Protein I as a Biomarker for Pancreatic Ductal Adenocarcinoma by Protein Biochip Technology".
Schwartz (1995) Clinica Chimica Acta 237:67-78 "Tissue cathepsins as tumor markers".
Shen (2004) Cancer Research 64:9018-9026 "Protein Expression Profiles in Pancreatic Adenocarcinoma Compared with Normal Pancreatic Tissue and Tissue Affected by Pancreatitis as Detected by Two-Dimensional Gel Electrophoresis and Mass Spectrometry".
Zeh (2005) Cancer Biomarkers 1:259-269 "Multianalyte profiling of serum cytokines for detection of pancreatic cancer".
European Search Report (Supplemental) dated Jul. 29, 2015 in EP 11874668.4.
Zelan et al. (2008) The Practical Journal of Cancer 23(4) "Common tumor biomarkers and researches on their use in detecting and diagnosing non-small cell lung cancer" [in Chinese and English Translation].
Acosta et al. (2000) PNAS 97(10):5450-5455 "Molecular basis for a link between complement and the vascular complications of diabetes".
Arikan et al. (2005) Journal of Cellular Physiology 204:139-145 "Induction of Macrophage Elastase (MMP-12) Gene Expression by Statins".
Bagnato et al. (2007) Molecular & Cellular Proteomics 6.6 1088-1102 "Proteomics Analysis of Human Coronary Atherosclerotic Plaque".
Bigalke et al. (2010) European Journal of Neurology 17:111-117 "Expression of platelet glycoprotein VI is associated with transient ischemic attack and stroke".
Bossi et al. (2009) Blood 113(15):3640-3648 "C7 is expressed on endothelial cells as a trap for the assembling terminal complement complex and may exert anti-inflammatory function".
Chiao et al. (2010) J Proteome Res. 9(5):2649-2657 "In vivo Matrix Metalloproteinase-7 Substrates Identified in the Left Ventricle Post-Myocardial Infarction Using Proteomics".
Chieng-Yane et al. (2010) JPET #175182 "Protease activated Receptor-1 antagonist, F 16618 reduces arterial restenosis by down-regulation of TNFα and MMP7 expression, and migration and proliferation of vascular smooth muscle cells".
Fam et al. (2010) Can J Cardiol 26(7):365-370 "Increased myocardial expression of angiopoietin-2 in patients undergoing urgent surgical revascularization for acute coronary syndromes".
Fiedler et al. (2004) Blood 103(11):4150-4156 "The Tie-2 ligand Angiopoietin-2 is stored in and rapidly released upon stimulation from endothelial cell Weibel-Palade bodies".
Fiedler et al. (2006) Nature Medicine 12(2):235-239 "Angiopoietin-2 sensitizes endothelial cells to TNF-α and has a crucial role in the induction of inflammation".
Fischetti et al. (2006) Autoimmunity 39(5):417-428 "Cross-talk between the complement system and endothelial cells in physiologic conditions and in vascular diseases".
Folsom et al. (2008) Metabolism Clinical and Experimental 57:1591-1596 "Variation in ANGPTL4 and risk of coronary heart disease: the Atherosclerosis Risk in Communities Study".
Gronski et al. (1997) The Journal of Biological Chemistry 272(18):12189-12194 "Hydrolysis of a Broad Spectrum of Extracellular Matrix Proteins by Human Macrophage Elastase".
Halberg et al. (2008) Endocrinol. Metab. Clin. North Am. 37(3):1-15 "The Adipocyte as an Endocrine Cell".
Hanash et al. (2008) Nature 452:571-579 "Mining the plasma proteome for cancer biomarkers".
Haskard et al. (2008) Current Opinion in Lipidology 19:478-482 "The role of complement in atherosclerosis".
Human Protoarray V2.0 Content List.
Invitrogen (2009) Immune Response Biomarker Profiling Service Report, p. 1-33 "Immune Response Biomarker Profiling on ProtoArray Human Protein Microarrays for Our Favorite Customer".
Jaumdally et al. (2009) Journal of Internal Medicine 267:385-393 "Effects of atorvastatin on circulating CD34+/CD133+/CD45—

(56) **References Cited**

OTHER PUBLICATIONS

progenitor cells and indices of angiogenesis (vascular endothelial growth factor and the angiopoietins 1 and 2) in atherosclerotic vascular disease and diabetes mellitus".

Jguirim-Souissi et al. (2007) American Journal of Cardiology 100:23-27 "Plasma Metalloproteinase-12 and Tissue Inhibitor of Metalloproteinase-1 Levels and Presence, Severity, and Outcome of Coronary Artery Disease".

Keefe et al. (2010) Nature Reviews Drug Discovery 9:537-550 "Aptamers as therapeutics".

Kim et al. (2006) Clinical Immunology 118:127-136 "Membrane complement regulatory proteins".

Kraaijeveld et al. (2007) Circulation 116:1931-1941 "CC Chemokine Ligand-5 (CCL5/RANTES) and CC Chemokine Ligand-18 (CCL18/PARC) Are Specific Markers of Refractory Unstable Angina Pectoris and Are Transiently Raised During Severe Ischemic Symptoms".

Langeggen et al. (2000) Clin. Exp. Immunol. 121:69-76 "The endothelium is an extrahepatic site of synthesis of the seventh component of the complement system".

Lee et al. (2011) Graefes Arch Clin Exp Ophthalmol 249:389-397 "Simvastatin suppresses expression of angiogenic factors in the retinas of rats with streptozotocin-induced diabetes".

Liang et al. (2006) Circulation 113:1993-2001 "Macrophage Metalloelastase Accelerates the Progression of Atherosclerosis in Transgenic Rabbits".

Lieb et al. (2010) Circ. Cardiovasc. Genet. 3:300-306 "Clinical and Genetic Correlates of Circulating Angiopoietin-2 and Soluble Tie-2 in the Community".

Lim et al. (2005) Atherosclerosis 180:113-118 "Angiopoietin-1 and angiopoietin-2 in diabetes mellitus: relationship to VEGF, glycaemic control, endothelial damage/dysfunction and atherosclerosis".

Mason et al. (2002) Circulation Research 91:696-703 "Statin-Induced Expression of Decay-Accelerating Factor Protects Vascular Endothelium Against Complement-Mediated Injury".

McNeill et al. (2010) Clinical Science 118:641-655 "Inflammatory cell recruitment in cardiovascular disease: murine models and potential clinical applications".

McPherron (2010) Immunol. Endocr. Metab. Agents Med. Chem. 10(4):217-231 "Metabolic Functions of Myostatin and GDF11".

Meltzer et al. (2010) Blood 116(1):113-121 "Venous thrombosis risk associated with plasma hypofibrinolysis is explained by elevated plasma levels of TAFI and PAI-1".

Meltzer et al., (2010) Blood, The American Society of Hematology, 116:529-536 "Plasma levels of fibrinolytic proteins and the risk of myocardial infarction in men".

Monahan et al. (1980) The Journal of Biological Chemistry 255(22):10579-10582 "Binding of the Eighth Component of Human Complement to the Soluble Cytolytic Complex Is Mediated by Its β Subunit".

Murphy et al. (1988) J. Clin. Invest. 81:1858-1864 "SP-40,40, a Newly Identified Normal Human Serum Protein Found in the SC5b-9 Complex of Complement and in the Immune Deposits in Glomerulonephritis".

Nagase et al. (2006) Cardiovascular Research 69:562-573 "Structure and function of matrix metalloproteinases and TIMPs".

Nomura et al. (2008) BBRC 365:863-869 "Skeletal muscle-derived progenitors capable of differentiating into cardiomyocytes proliferate through myostatin-independent TGF-β family signaling".

Okamoto et al. (2002) The FASEB Journal 10 "Angiogenesis induced by advanced glycation end products and its prevention by cerivastatin".

Page-McCaw et al. (2007) Molecular Cell Biology 8:221-233 "Matrix metalloproteinases and the regulation of tissue remodelling".

Peden et al. (2011) Nature Genetics 43(4) 339-44 "A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease".

Peden et al. Nature Genetics doi:10.1038/ng.782 "A genome-wide association study in Europeans and South Asians identifies five novel loci for coronary artery disease".

Podack et al. (1978) The Journal of Immunology 120(6):1841-1848 "The C5b-6 Complex: Formation, Isolation, and Inhibition of its Activity by Lipoprotein and the S-Protein of Human Serum".

ProtoArray (2009) Human ProtoArray 2.0 Content List, 1.

Raitoharju et al. (2011) Atherosclerosis 219:211-217 "miR-21, miR-210, miR-34a, and miR-146a/b are up-regulated in human atherosclerotic plaques in the Tampere Vascular Study".

Raitoharju et al. (2011) Atherosclerosis 219:211-217 Supplementary tables "miR-21, miR-210, miR-34a, and miR-146a/b are up-regulated in human atherosclerotic plaques in the Tampere Vascular Study".

Reape et al. (1999) American Journal of Pathology 154(2):365-374 "Expression and Cellular Localization of the CC Chemokines PARC and ELC in Human Atherosclerotic Plaques".

Rivera et al. (2009) Haematologica 94(5):700-711 "Platelet receptors and signaling in the dynamics of thrombus formation".

Robertson et al. (2012) BBRC 427:568-573 "Synexpression group analyses identify new functions of FSTL3, a TGFβ ligand inhibitor".

Siddiqui et al. (2004) Journal of Molecular and Cellular Cardiology 37:1235-1244 "Simvastatin enhances myocardial angiogenesis induced by vascular endothelial growth factor gene transfer".

Smart-Halajko et al. (2010) Supplemental Material "The relationship between plasma angiopoietin-like protein 4 (Angptl4) levels, ANGPTL4 genotype and coronary heart disease risk".

Souza et al. (2008) Molecular Endocrinology 22(12):2689-2702 "Proteomic Identification and Functional Validation of Activins and Bone Morphogenetic Protein 11 as Candidate Novel Muscle Mass Regulators".

Speidl et al. (2011) Journal of Thrombosis and Haemostasis 9:428-440 "Complement in atherosclerosis: friend or foe?"

Stejskal et al. (2008) Gen. Physiol. Biophys. 27:59-63 "Angiopoietin-like protein 4: development, analytical characterization, and clinical testing of a new ELISA".

Sukonina et al. (2006) PNAS 103(46):17450-17455 "Angiopoietin-like protein 4 converts lipoprotein lipase to inactive monomers and modulates lipase activity in adipose tissue".

Swinnen et al. (2009) "Absence of Thrombospondin-2 Causes Age-Related Dilated Cardiomyopathy", Circulation, Journal of the American Heart Association 120:1585-1597.

Takahashi et al. (2012) Heart Vessels 27:337-343 "Prospective, randomized, single-blind comparison of effects of 6 months' treatment with atorvastatin versus pravastatin on leptin and angiogenic factors in patients with coronary artery disease".

Talmud et al. (2008) Thromb. Vasc. Biol. 28:2319-2325 "ANGPTL4 E40K and T266M Effects on Plasma Triglyceride and HDL Levels, Postprandial Responses, and CHD Risk".

Talmud et al. (2008) Thromb. Vasc. Biol. 28:2319-2325 Supplementary methods "ANGPTL4 E40K and T266M Effects on Plasma Triglyceride and HDL Levels, Postprandial Responses, and CHD Risk".

Tedesco et al. (1997) J. Exp. Med 185(9):1619-1627 "The Cytolytically Inactive Terminal Complement Complex Activates Endothelial Cells to Express Adhesion Molecules and Tissue Factor Procoagulant Activity".

Théroux et al. (2006) Can. J. Cardiol. 22(Suppl B):18B-24B "Complement activity and pharmacological inhibition in cardiovascular disease".

Ulrich et al. (2009) Cytometry Part A 75A(9):727-733 "Disease-specific biomarker discovery by aptamers".

Van Almen et al. (2011) Journal of Molecular and Cellular Cardiology 51:318-328 "Absence of thrombospondin-2 increases cardiomyocyte damage and matrix disruption in doxorubicin-induced cardiomyopathy".

Wang et al. (2011) Biomedicine & Pharmacotherapy 65:118-122 "The effect of atorvastatin on mRNA levels of inflammatory genes expression in human peripheral blood lymphocytes by DNA micro array".

Wang et al. (2009) Circulation, Journal of the American Heart Association 119:2480-2489 "Matrix Metalloproteinase-7 and ADAM-

(56) **References Cited**

OTHER PUBLICATIONS

12 (a Disintegrin and Metalloproteinase-12) Define a Signaling Axis in Agonist-Induced Hypertension and Cardiac Hypertrophy".
Wang et al. (2009) MMP-7 and ADAM 12 define a signalling axis in agonist-induced hypertension and cardiac hypertrophy, Supplemental Material.
Wang et al. (2010) Journal of Human Genetics 55:490-494 "Common polymorphisms in ITGA2, PON1 and THBS2 are associated with coronary atherosclerosis in a candidate gene association study of the Chinese Han population".
Yao et al. (2007) The Journal of Biological Chemistry 282(42):31038-31045 "High Glucose Increases Angiopoietin-2 Transcription in Microvascular Endothelial Cells through Methylglyoxal Modification of mSin3A".
Yasojima et al. (2001) American Journal of Pathology 158(3): 1039-1051 "Generation of C-Reactive Protein and Complement Components in Atherosclerotic Plaques".
Yasojima et al. (2001) Arterioscler Thromb Vasc Biol. 21:1214-1219 "Complement Components, but Not Complement Inhibitors, Are Upregulated in Atherosclerotic Plaques".

* cited by examiner

FIG. 1A

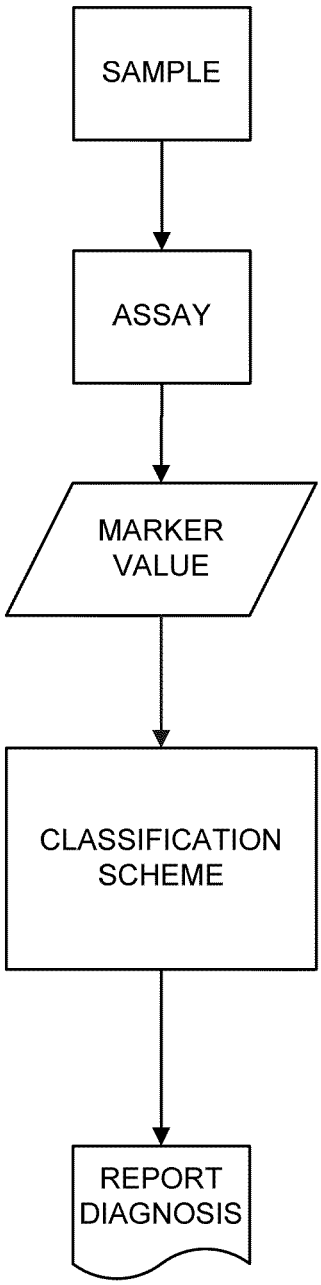

SAMPLE
ASSAY
MARKER VALUE
CLASSIFICATION SCHEME
REPORT DIAGNOSIS

FIG. 1B

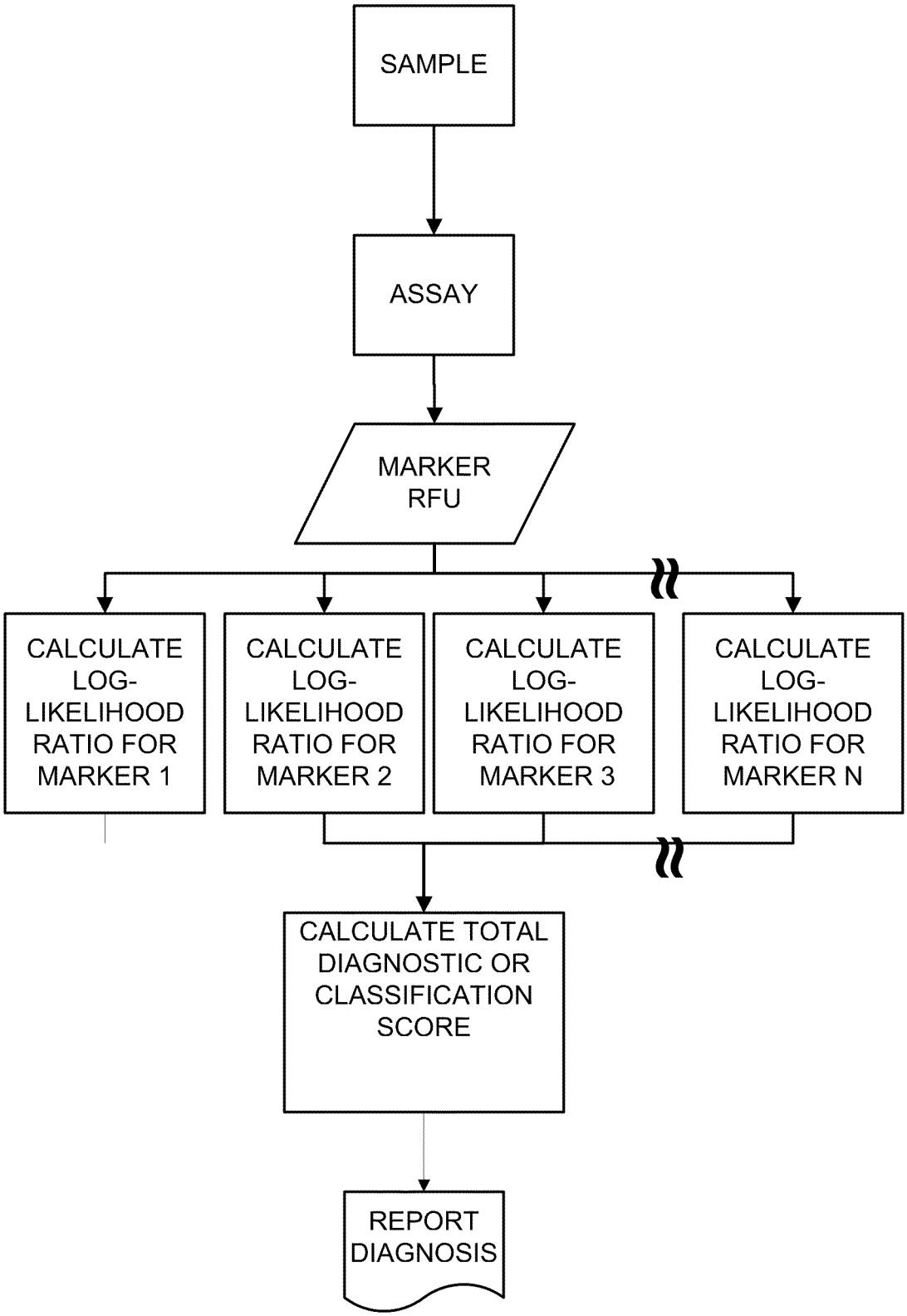

SAMPLE
ASSAY
MARKER RFU
CALCULATE LOG-LIKELIHOOD RATIO FOR MARKER 1
CALCULATE LOG-LIKELIHOOD RATIO FOR MARKER 2
CALCULATE LOG-LIKELIHOOD RATIO FOR MARKER 3
CALCULATE LOG-LIKELIHOOD RATIO FOR MARKER N
CALCULATE TOTAL DIAGNOSTIC OR CLASSIFICATION SCORE
REPORT DIAGNOSIS

FIG. 2

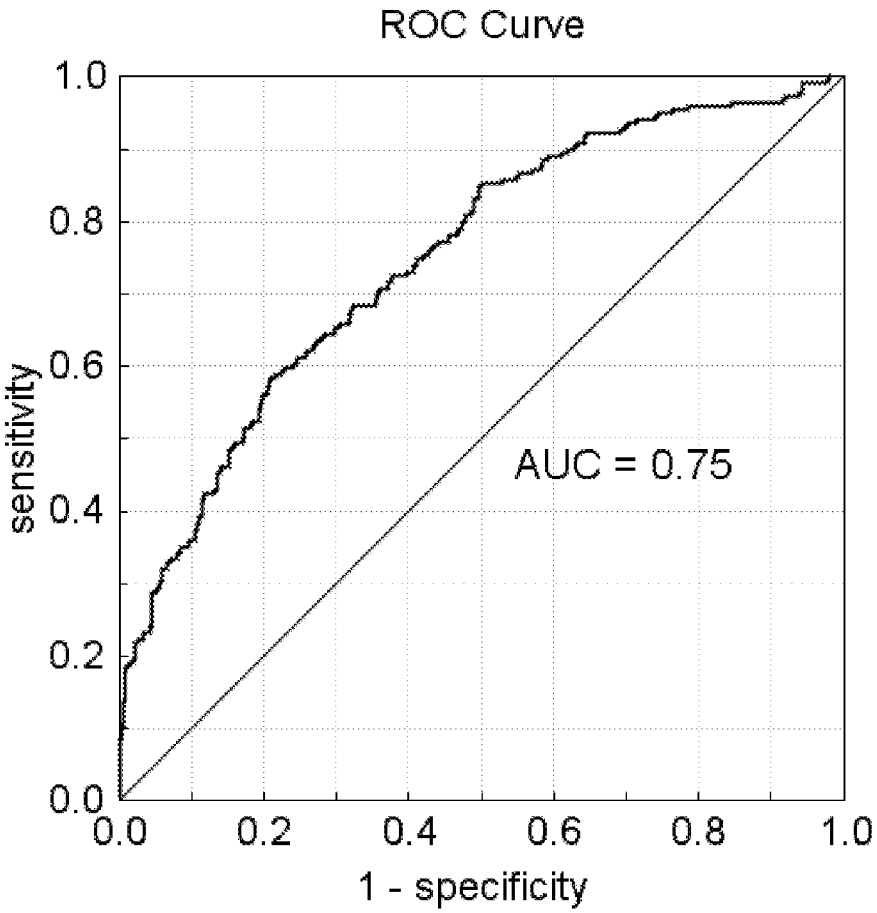

ROC Curve
1.0
0.8
0.6
0.4
0.2
0.0
sensitivity
AUC = 0.75
0.0
0.2
0.4
0.6
0.8
1.0
1 - specificity

FIG. 3

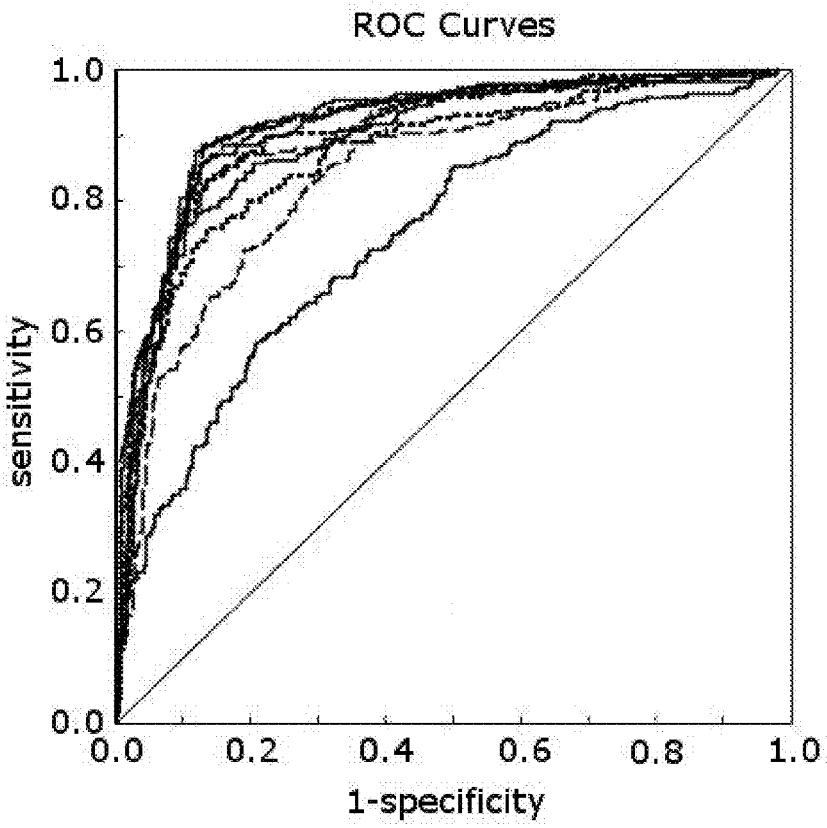


FIG. 4

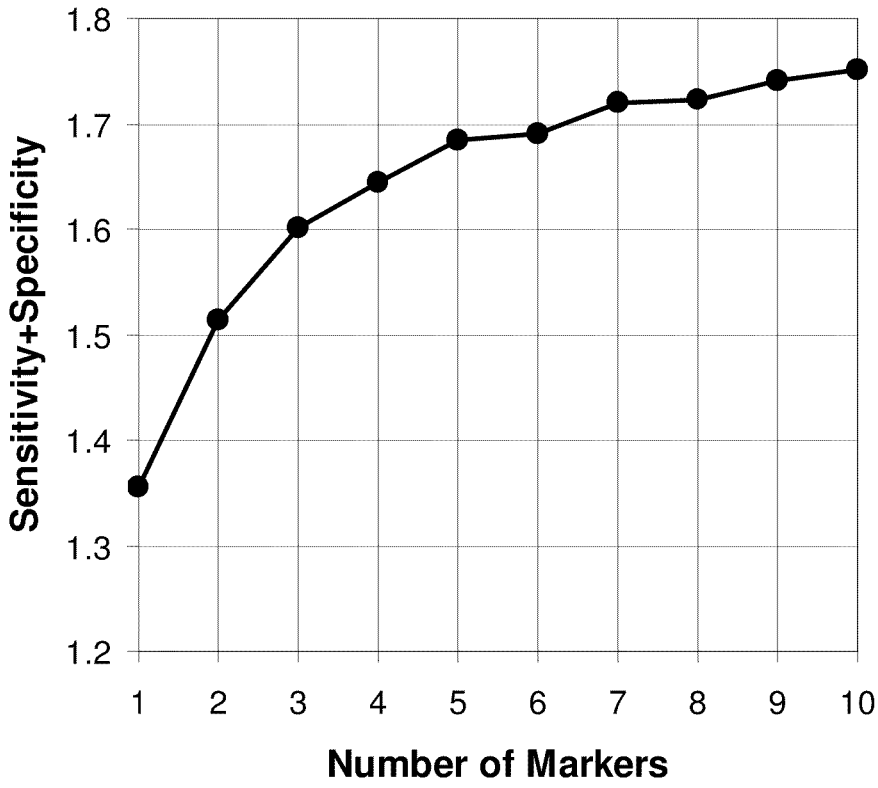

1.8
1.7
1.6
1.5
1.4
1.3
1.2
Sensitivity+Specificity
1
2
3
4
5
6
7
8
9
10
Number of Markers

FIG. 5

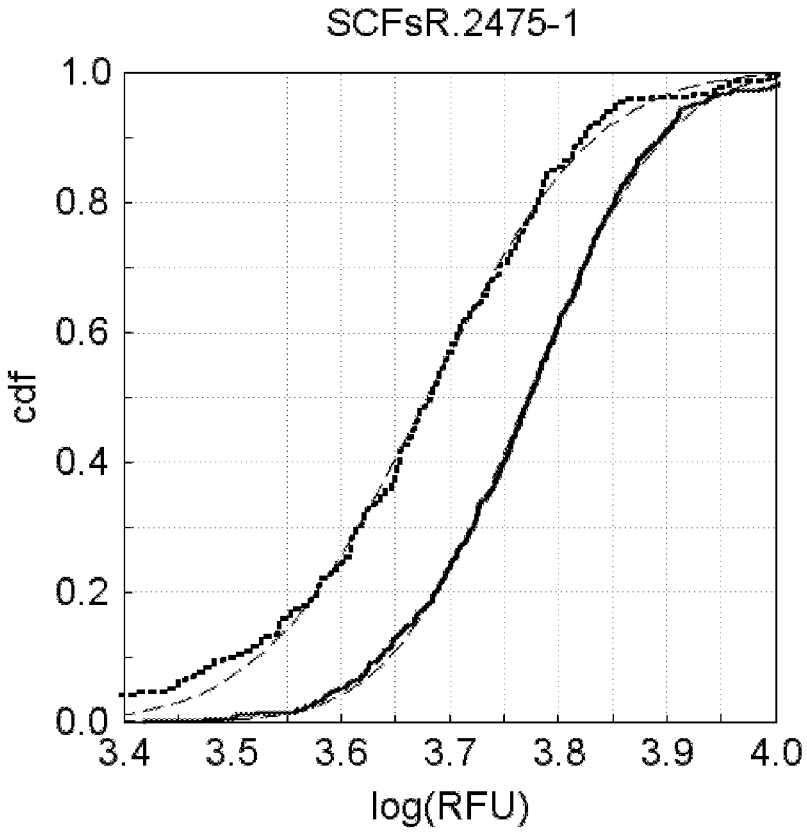


FIG. 6

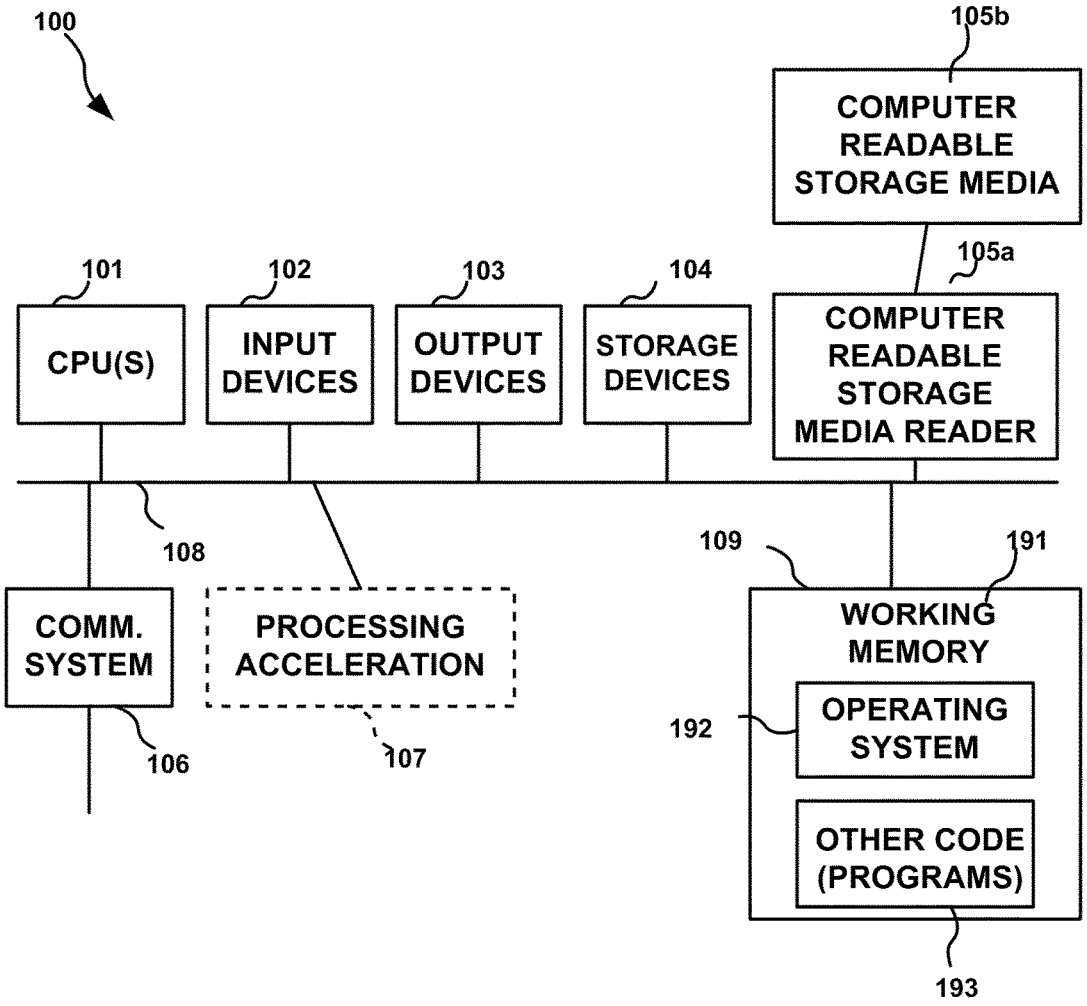

100
105b
COMPUTER READABLE STORAGE MEDIA
105a
101
102
103
104
CPU(S)
INPUT DEVICES
OUTPUT DEVICES
STORAGE DEVICES
COMPUTER READABLE STORAGE MEDIA READER
108
109
191
COMM. SYSTEM
PROCESSING ACCELERATION
WORKING MEMORY
192
OPERATING SYSTEM
OTHER CODE (PROGRAMS)
106
107
193

FIG. 7

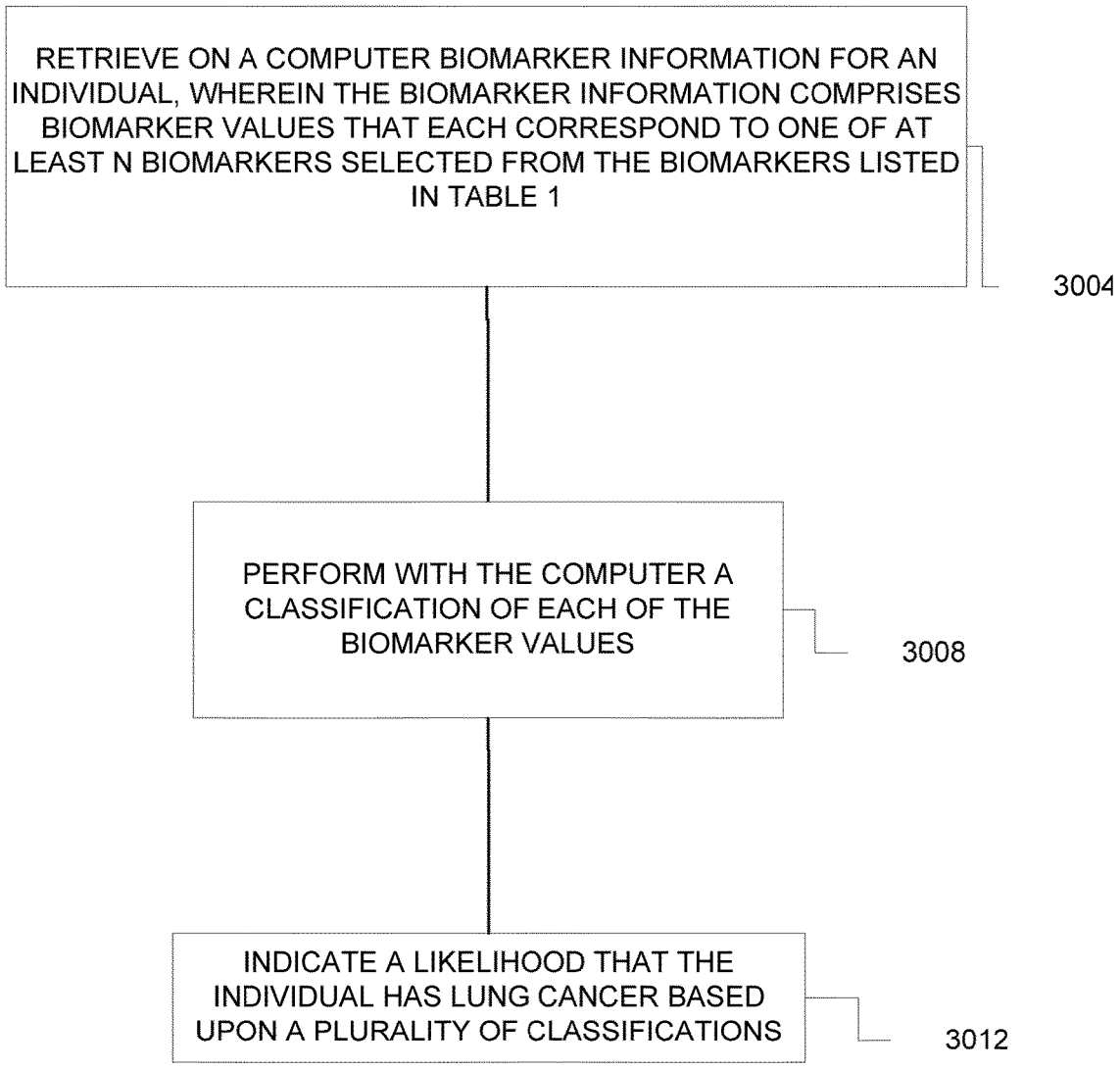

RETRIEVE ON A COMPUTER BIOMARKER INFORMATION FOR AN INDIVIDUAL, WHEREIN THE BIOMARKER INFORMATION COMPRISES BIOMARKER VALUES THAT EACH CORRESPOND TO ONE OF AT LEAST N BIOMARKERS SELECTED FROM THE BIOMARKERS LISTED IN TABLE 1
3004
PERFORM WITH THE COMPUTER A CLASSIFICATION OF EACH OF THE BIOMARKER VALUES
3008
INDICATE A LIKELIHOOD THAT THE INDIVIDUAL HAS LUNG CANCER BASED UPON A PLURALITY OF CLASSIFICATIONS
3012
3000

FIG. 8

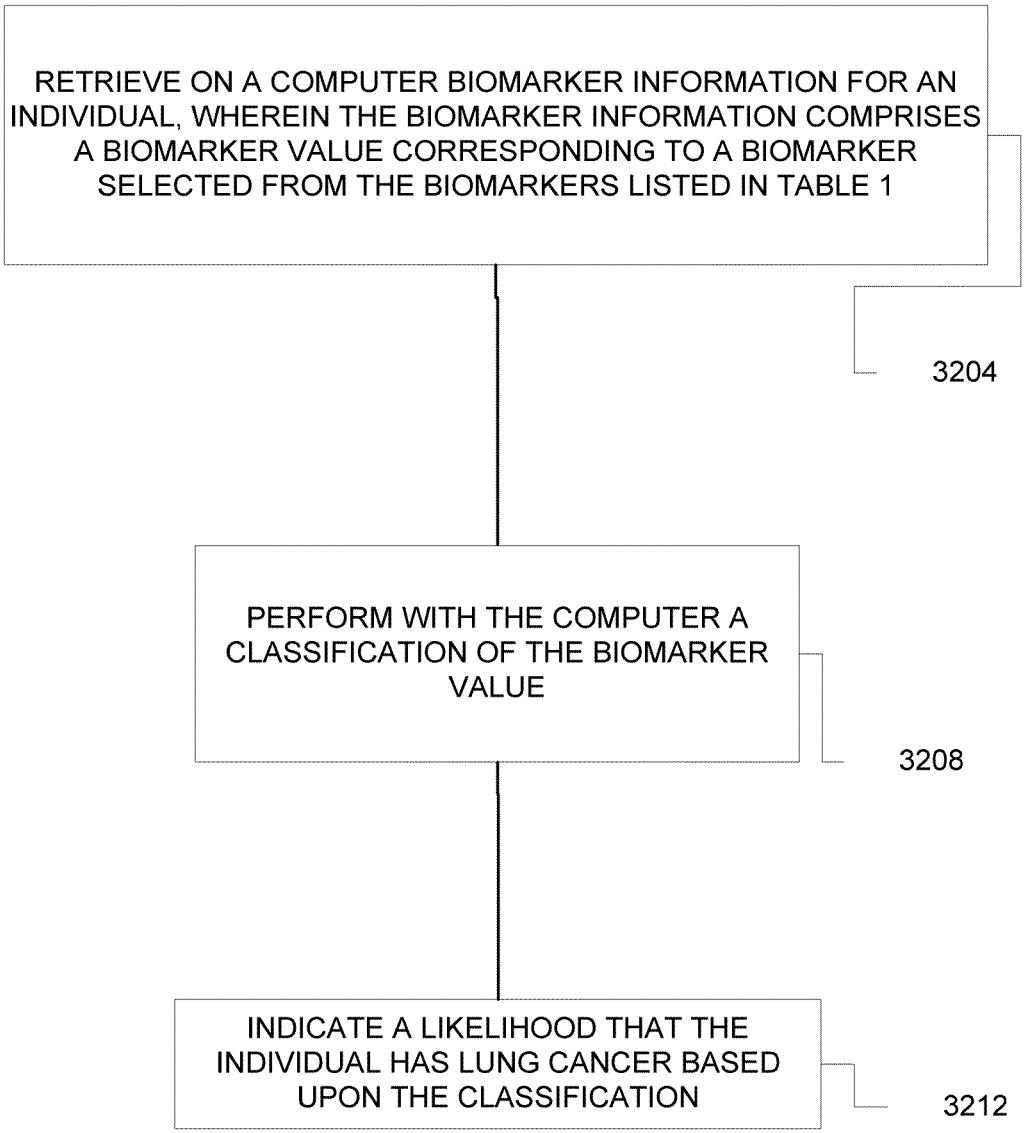
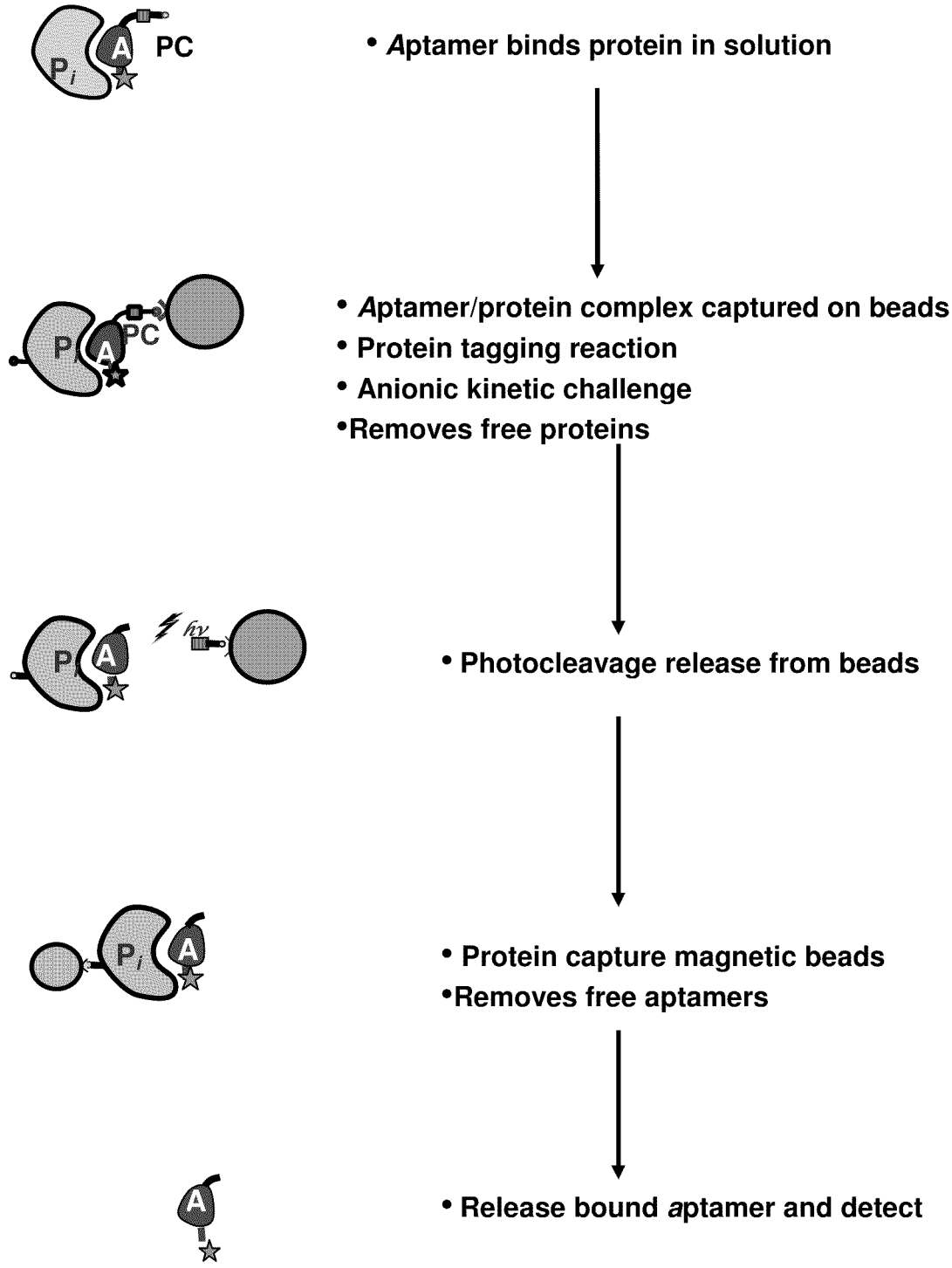

RETRIEVE ON A COMPUTER BIOMARKER INFORMATION FOR AN INDIVIDUAL, WHEREIN THE BIOMARKER INFORMATION COMPRISES A BIOMARKER VALUE CORRESPONDING TO A BIOMARKER SELECTED FROM THE BIOMARKERS LISTED IN TABLE 1
3204
PERFORM WITH THE COMPUTER A CLASSIFICATION OF THE BIOMARKER VALUE
3208
INDICATE A LIKELIHOOD THAT THE INDIVIDUAL HAS LUNG CANCER BASED UPON THE CLASSIFICATION
3212
3200

FIG. 9


PC
• Aptamer binds protein in solution
• Aptamer/protein complex captured on beads
• Protein tagging reaction
• Anionic kinetic challenge
•Removes free proteins
hν
• Photocleavage release from beads
• Protein capture magnetic beads
•Removes free aptamers
• Release bound aptamer and detect

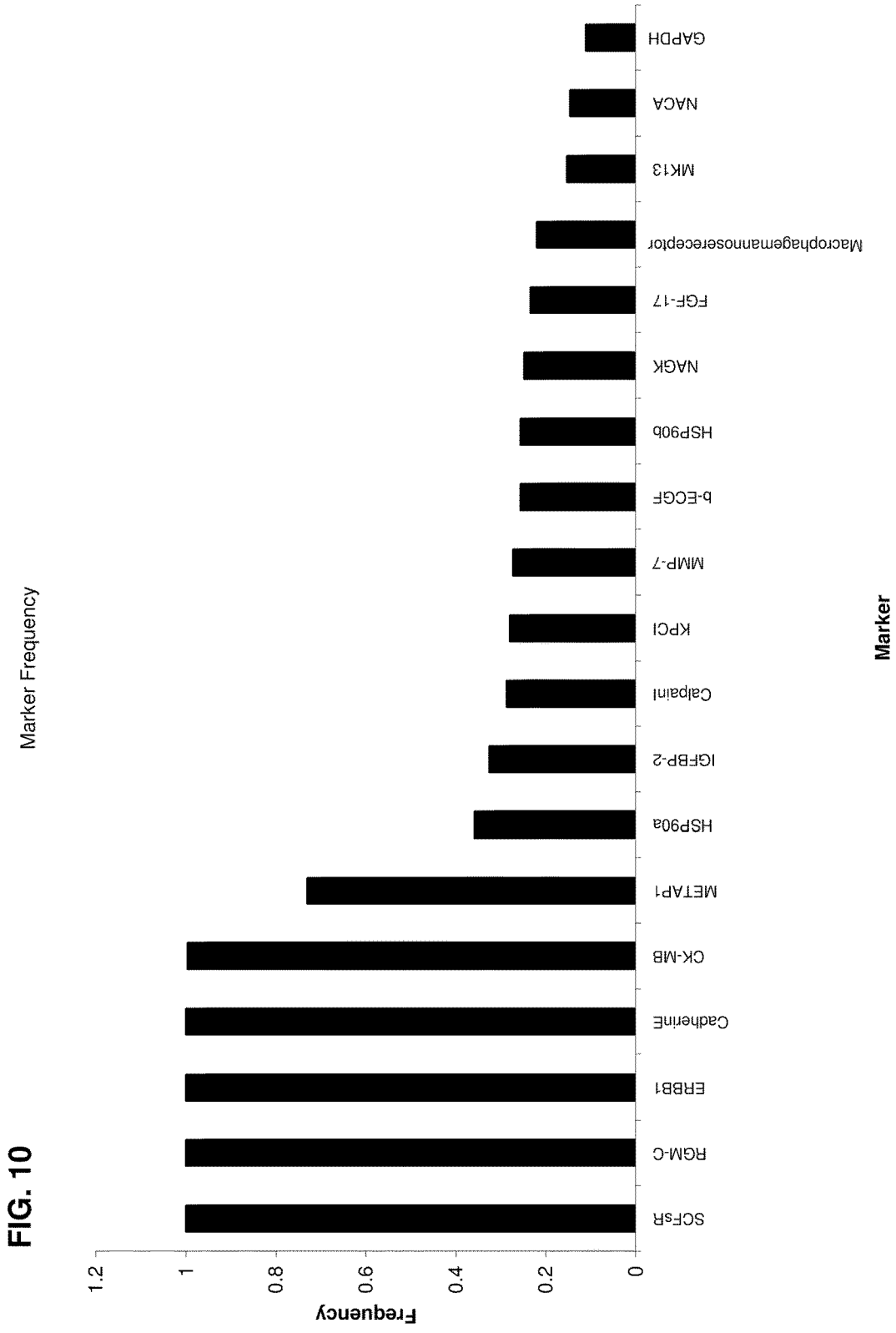

Marker Frequency
Frequency
1.2
1
0.8
0.6
0.4
0.2
0
SCFsR
RGM-C
ERBB1
Cadherine
CK-MB
METAP1
HSP90a
IGFBP-2
Calpain1
KPCI
MMP-7
b-ECGF
HSP90b
NAGK
FGF-17
Macrophagemannosereceptor
MK13
NACA
GAPDH
Marker

FIG. 10

FIG. 11

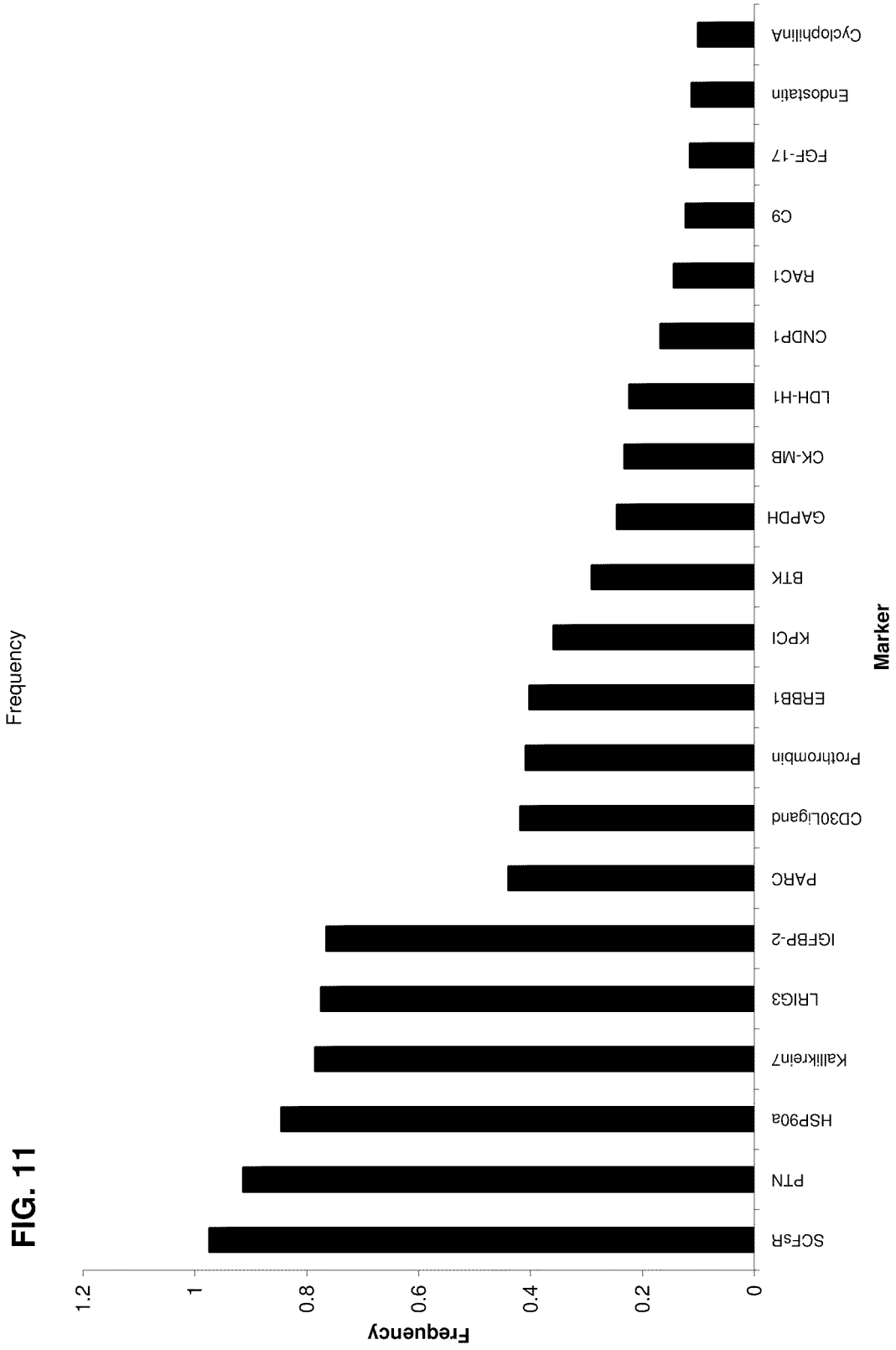

Frequency
1.2
1
0.8
0.6
0.4
0.2
0
SCFsR
PTN
HSP90a
Kallikrein7
LRIG3
IGFBP-2
PARC
CD30Ligand
Prothrombin
ERBB1
KPCI
BTK
GAPDH
CK-MB
LDH-H1
CNDP1
RAC1
C9
FGF-17
Endostatin
CyclophilinA
Marker

FIG. 12

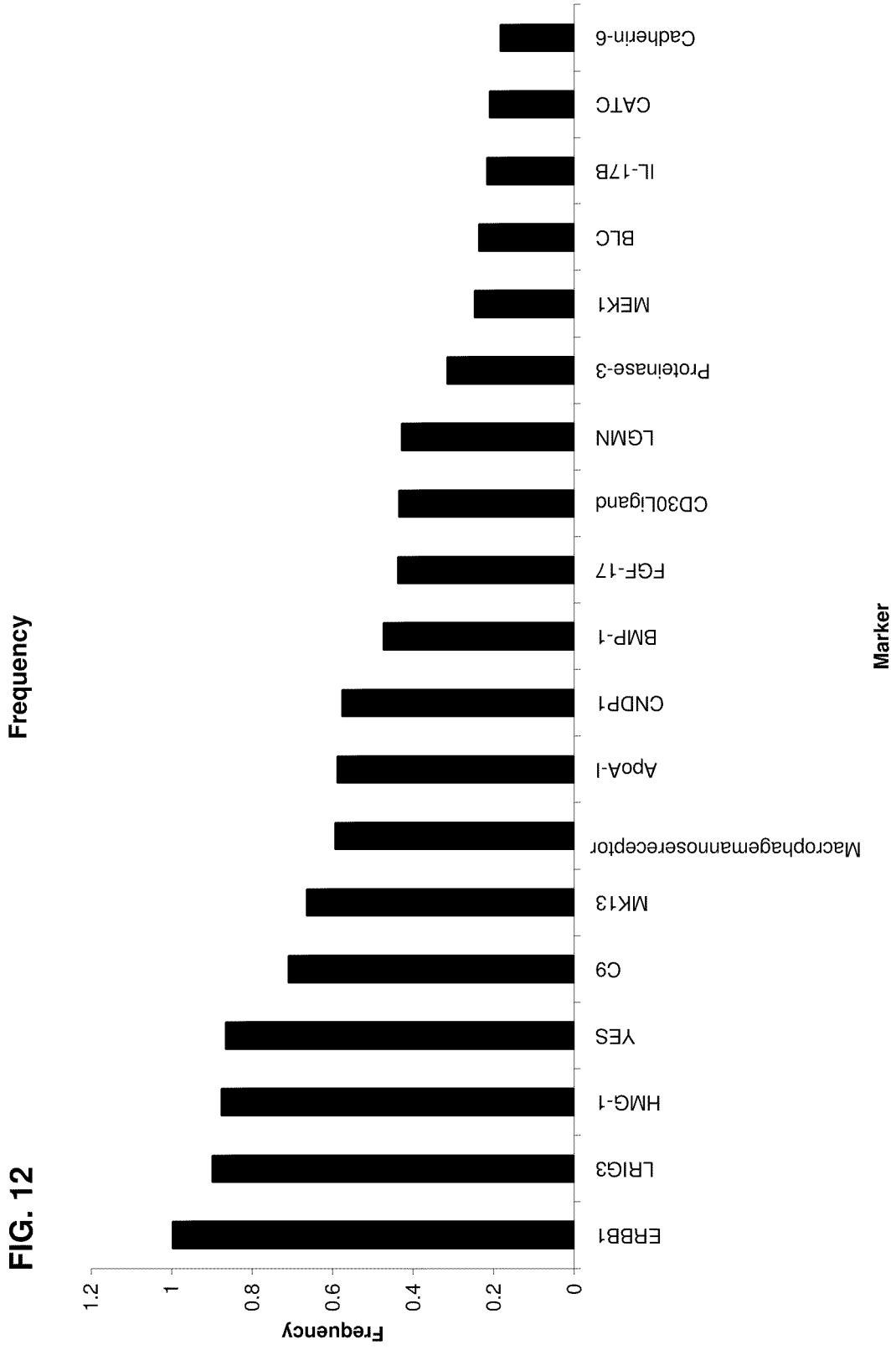
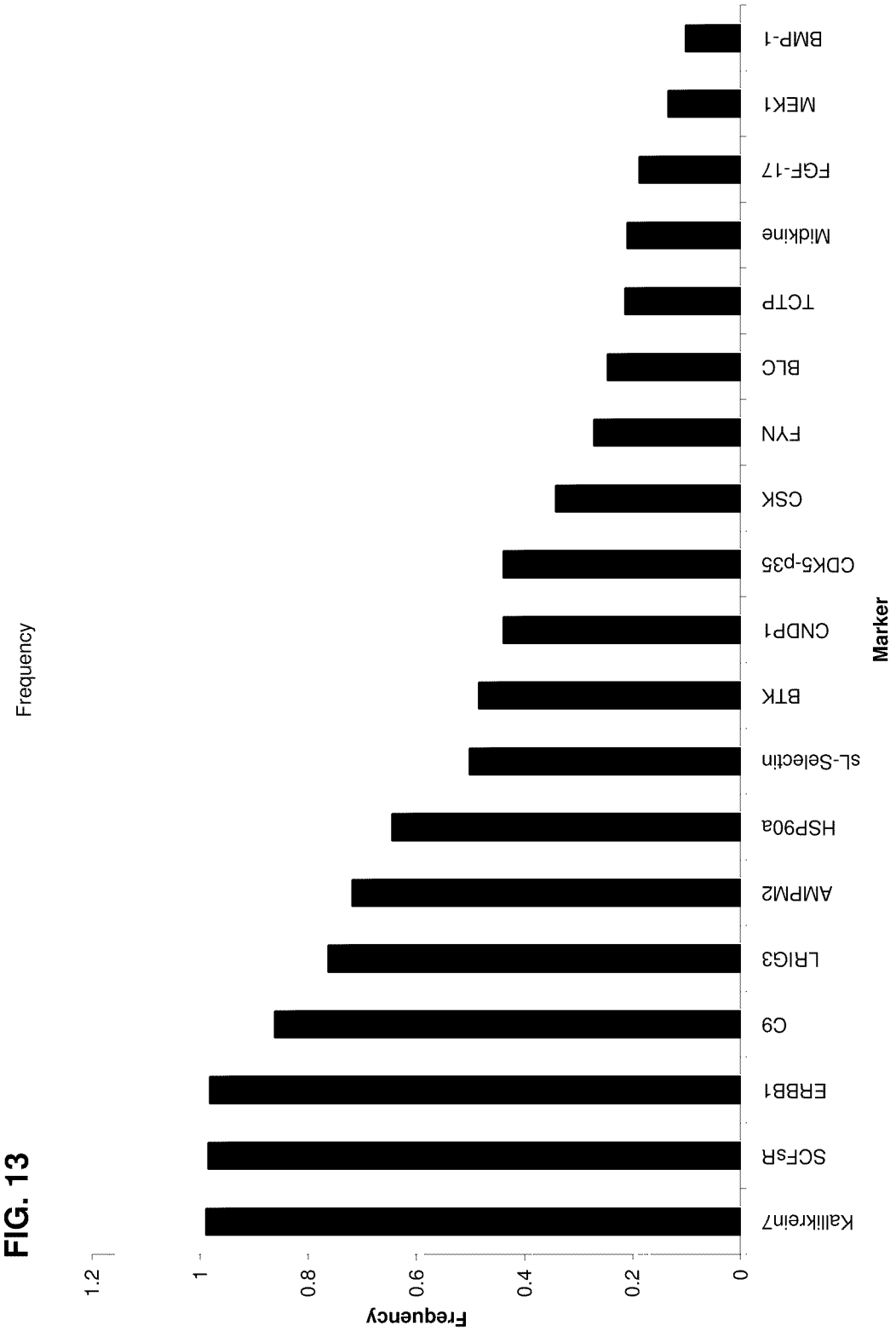

Frequency
1.2
1
0.8
0.6
0.4
0.2
0
Frequency
ERBB1
LRIG3
HMG-1
YES
C9
MK13
Macrophagemannosereceptor
ApoA-I
CNDP1
BMP-1
FGF-17
CD30Ligand
LGMN
Proteinase-3
MEK1
BLC
IL-17B
CATC
Cadherin-6
Marker

FIG. 13


Frequency
1.2
1
0.8
0.6
0.4
0.2
0
Kallikrein7
SCFsR
ERBB1
C9
LRIG3
AMPM2
HSP90a
sL-Selectin
BTK
CNDP1
CDK5-p35
CSK
FYN
BLC
TCTP
Midkine
FGF-17
MEK1
BMP-1
Marker

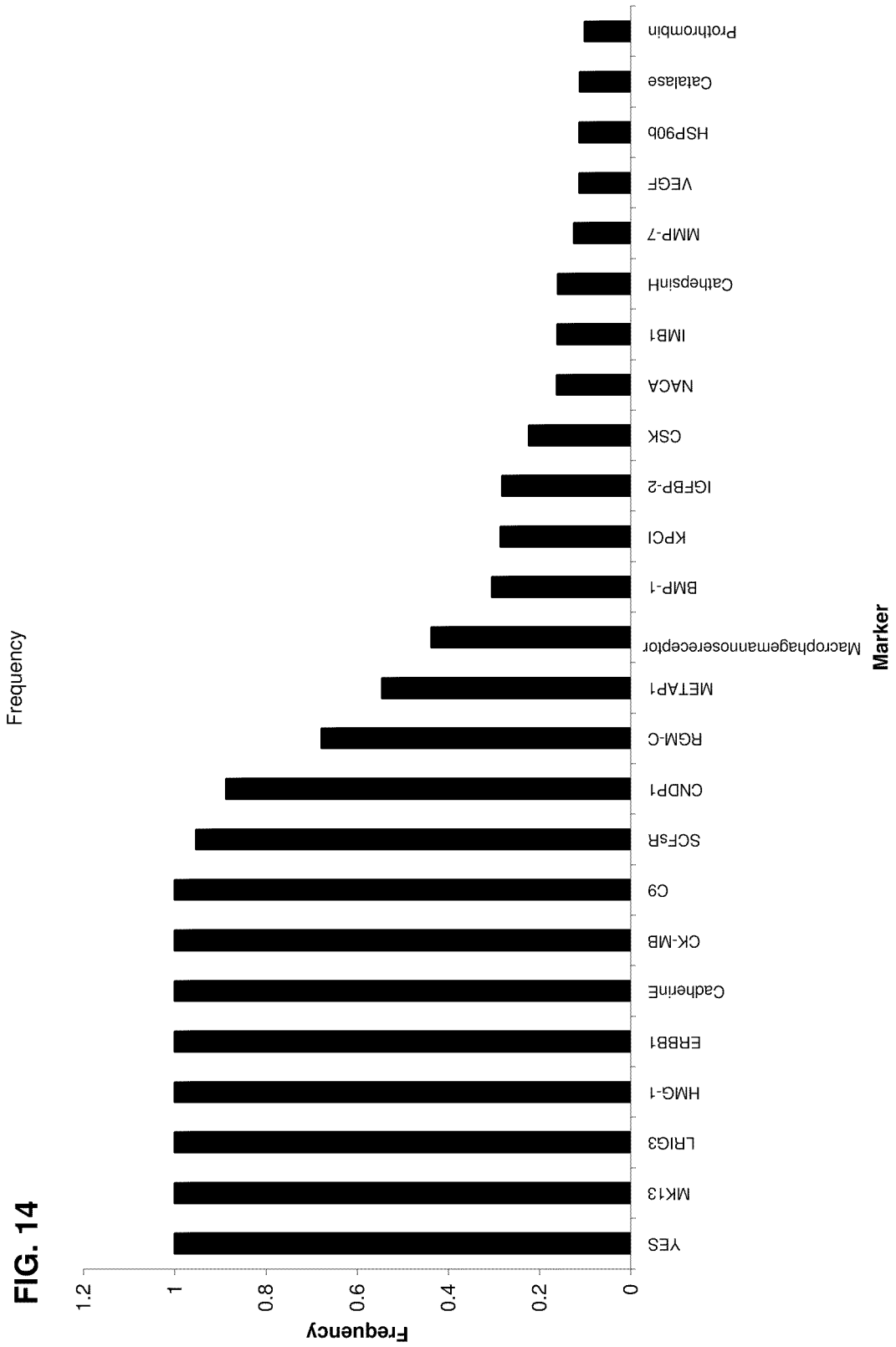

Frequency
1.2
1
0.8
0.6
0.4
0.2
0
Frequency
YES
MK13
LRIG3
HMG-1
ERBB1
Cadherin E
CK-MB
C9
SCFsR
CNDP1
RGM-C
METAP1
Macrophagemannosereceptor
BMP-1
KPCI
IGFBP-2
CSK
NACA
IMB1
Cathepsin H
MMP-7
VEGF
HSP90b
Catalase
Prothrombin
Marker

FIG. 14

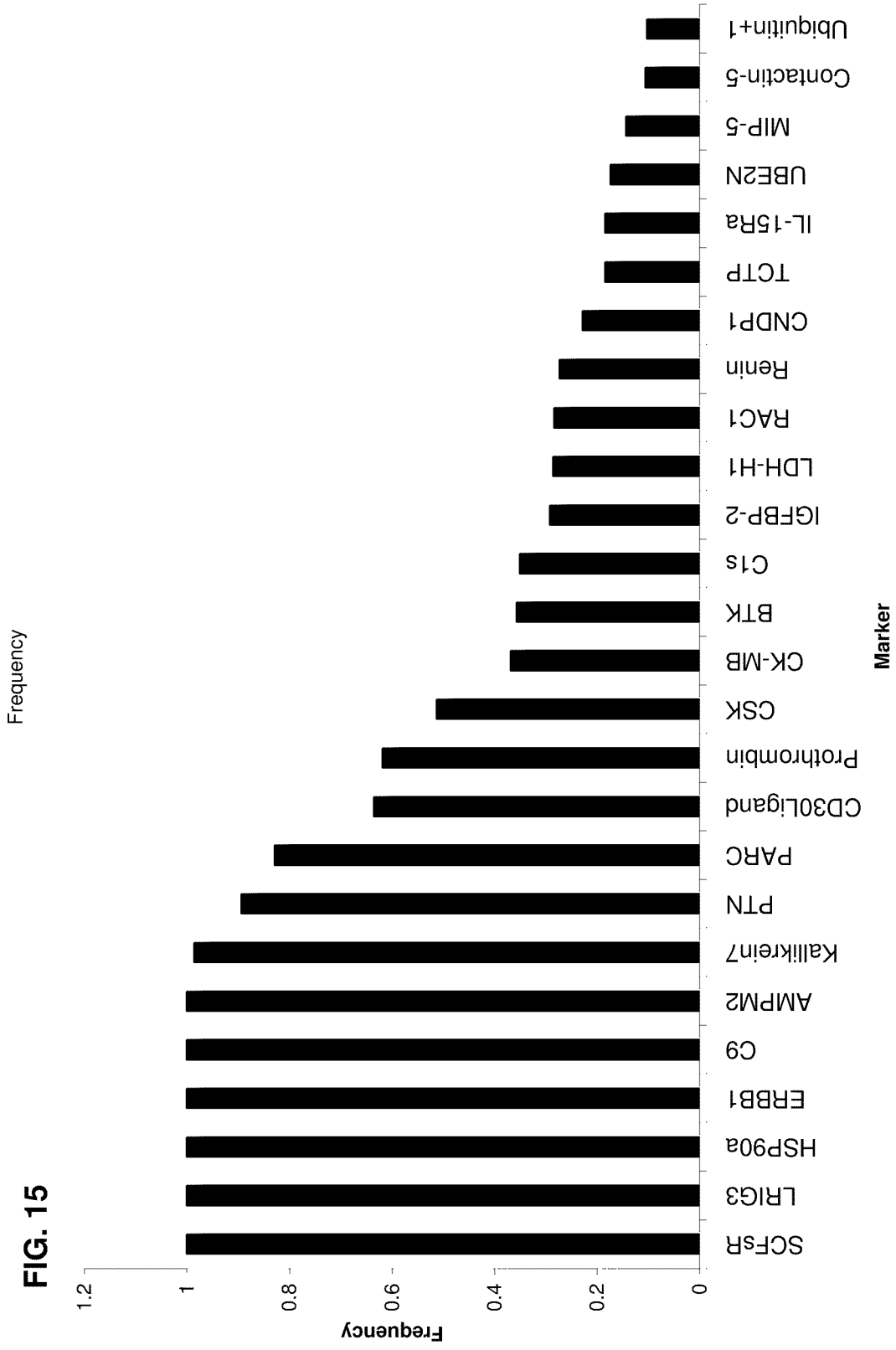

Frequency
1.2
1
0.8
0.6
0.4
0.2
0
Frequency
SCFsR
LRIG3
HSP90a
ERBB1
C9
AMPM2
Kallikrein7
PTN
PARC
CD30Ligand
Prothrombin
CSK
CK-MB
BTK
C1s
IGFBP-2
LDH-H1
RAC1
Renin
CNDP1
TCTP
IL-15Ra
UBE2N
MIP-5
Contactin-5
Ubiquitin+1
Marker

FIG. 15

FIG. 16

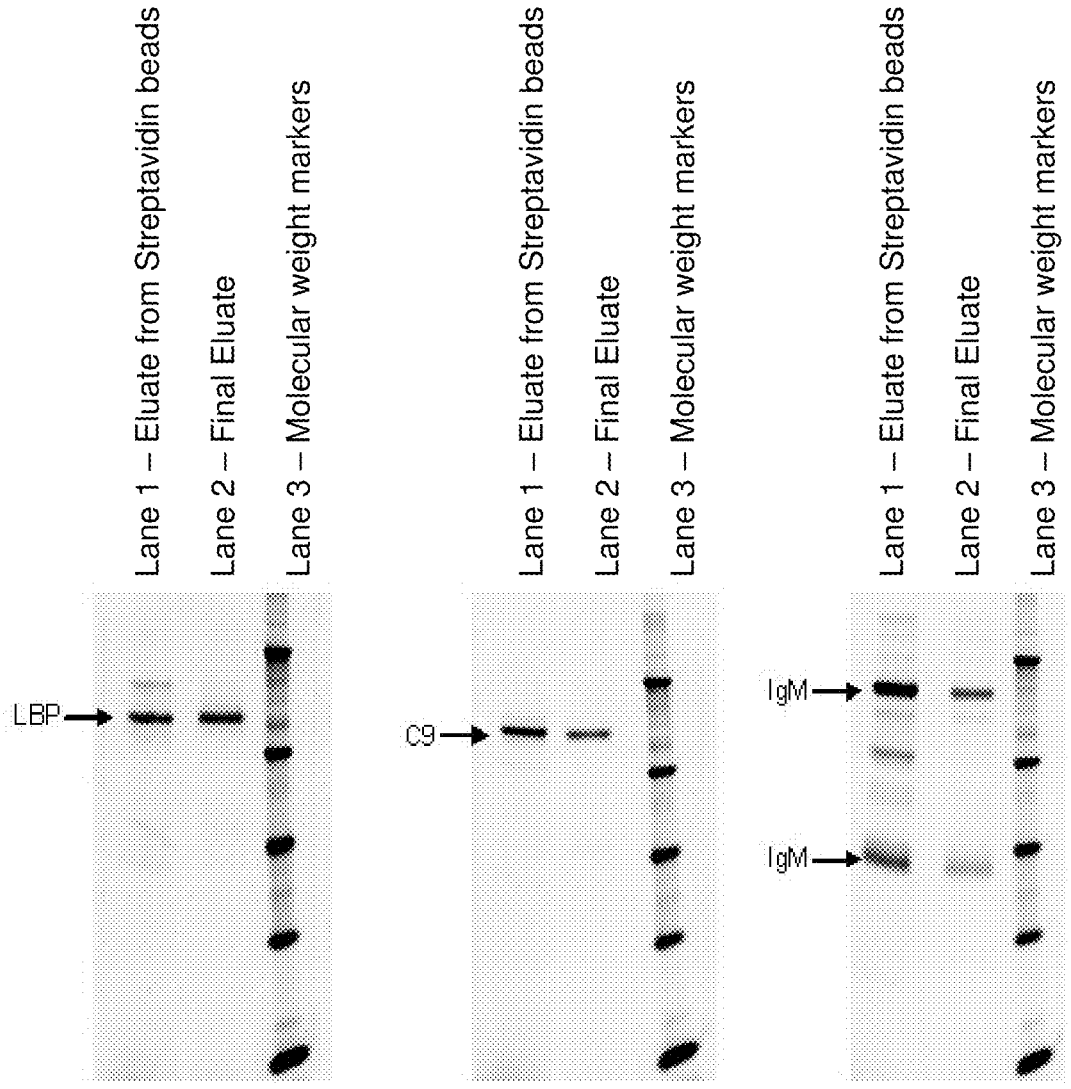

Lane 1 – Eluate from Streptavidin beads
Lane 2 – Final Eluate
Lane 3 – Molecular weight markers
LBP
Lane 1 – Eluate from Streptavidin beads
Lane 2 – Final Eluate
Lane 3 – Molecular weight markers
C9
Lane 1 – Eluate from Streptavidin beads
Lane 2 – Final Eluate
Lane 3 – Molecular weight markers
IgM
IgM

FIG. 17C

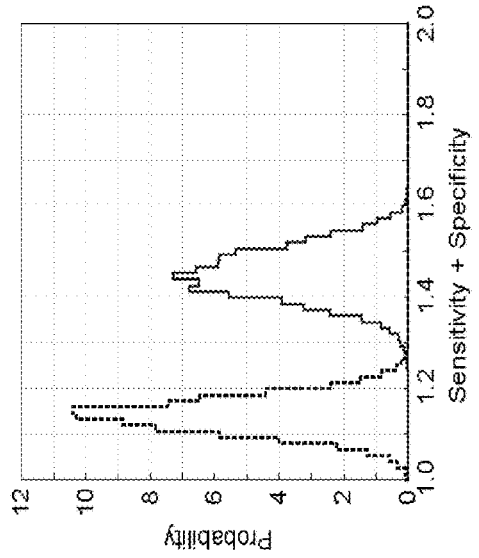


FIG. 17B

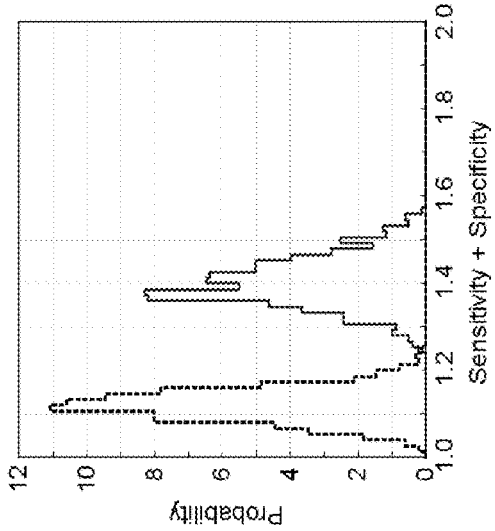


FIG. 17A

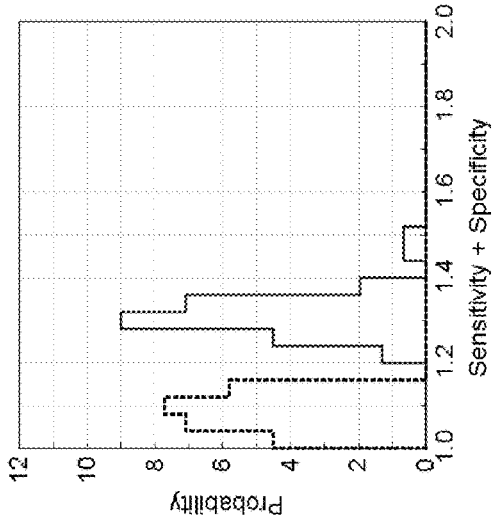


FIG. 18C

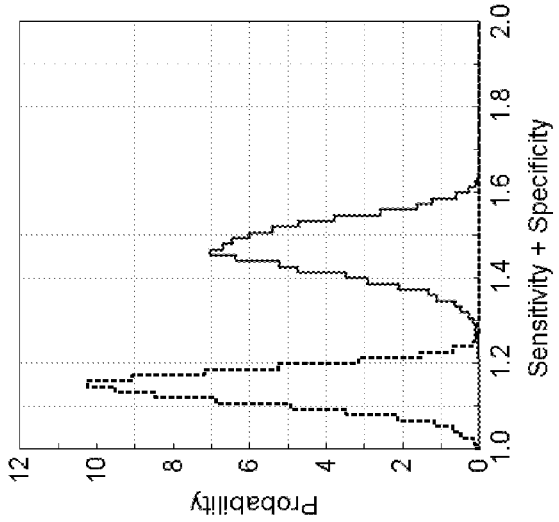


FIG. 18B

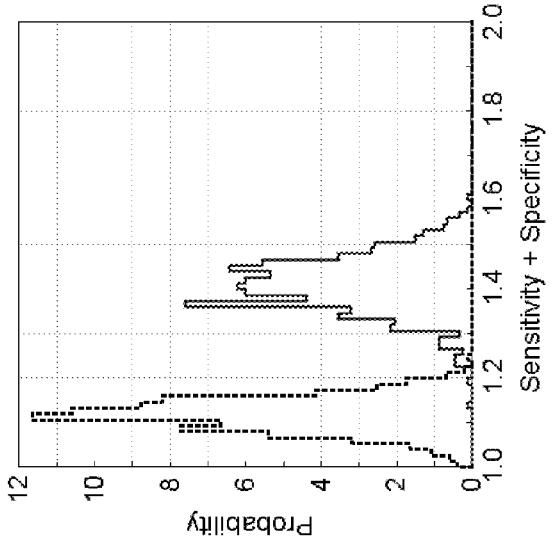


FIG. 18A

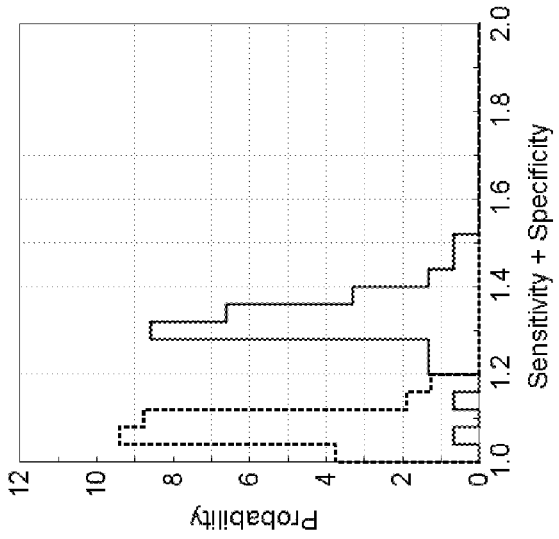


FIG. 19A

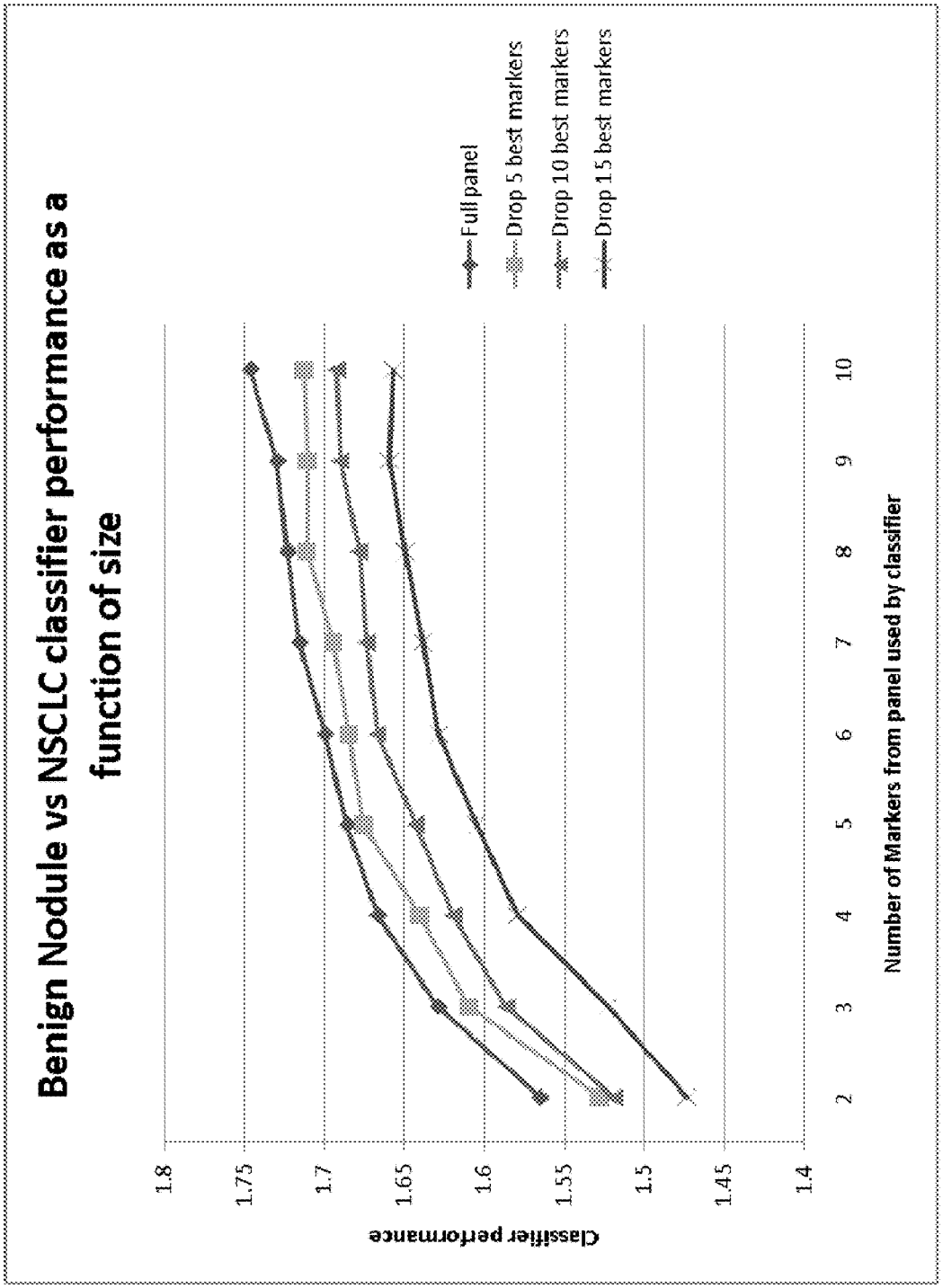

Benign Nodule vs NSCLC classifier performance as a function of size
Full panel
Drop 5 best markers
Drop 10 best markers
Drop 15 best markers
Classifier performance
1.8
1.75
1.7
1.65
1.6
1.55
1.5
1.45
1.4
2
3
4
5
6
7
8
9
10
Number of Markers from panel used by classifier

FIG. 19B

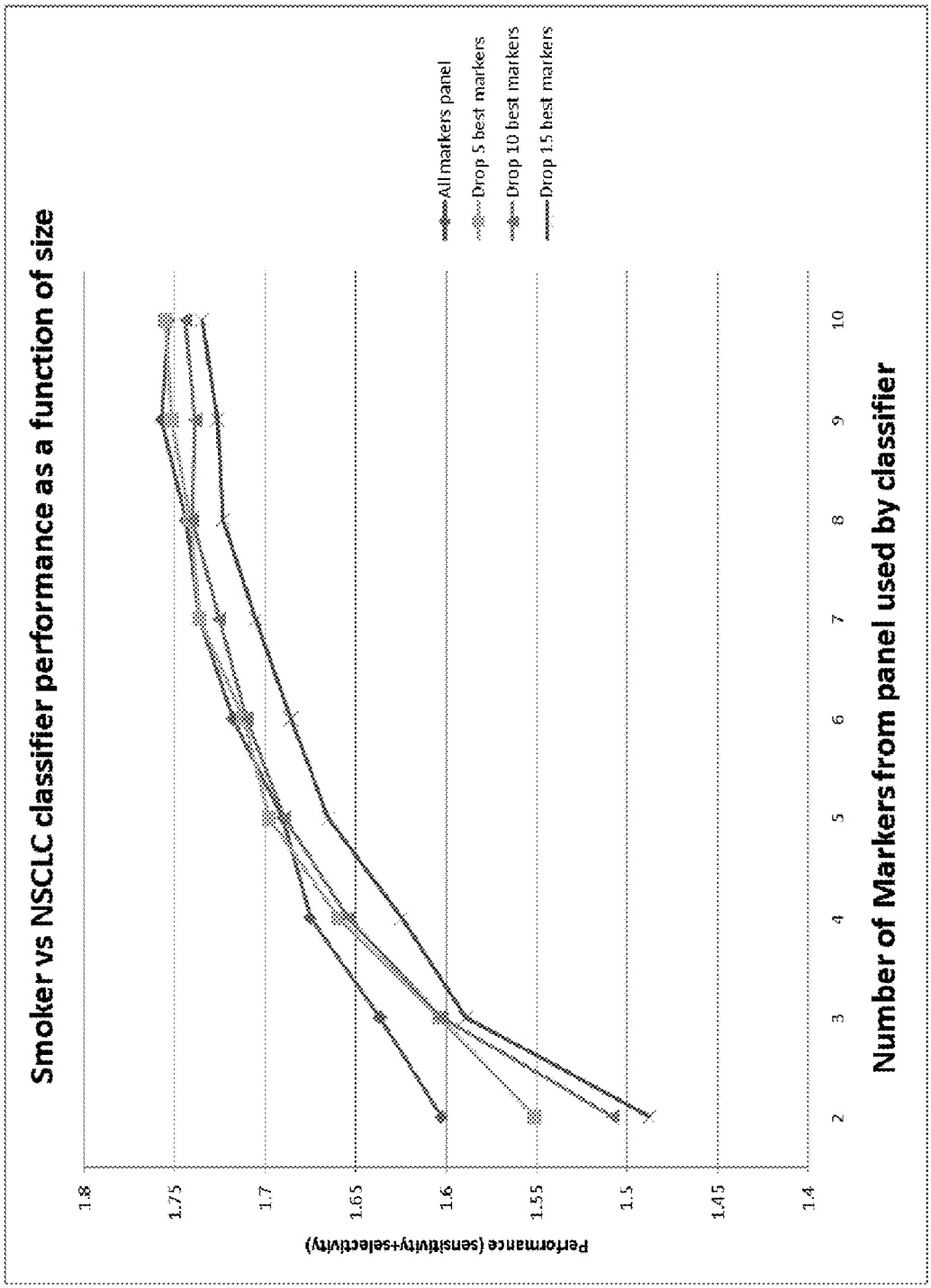

Smoker vs NSCLC classifier performance as a function of size
All markers panel
Drop 5 best markers
Drop 10 best markers
Drop 15 best markers
Performance (sensitivity+selectivity)
1.8
1.75
1.7
1.65
1.6
1.55
1.5
1.45
1.4
2
3
4
5
6
7
8
9
10
Number of Markers from panel used by classifier

FIG 20B

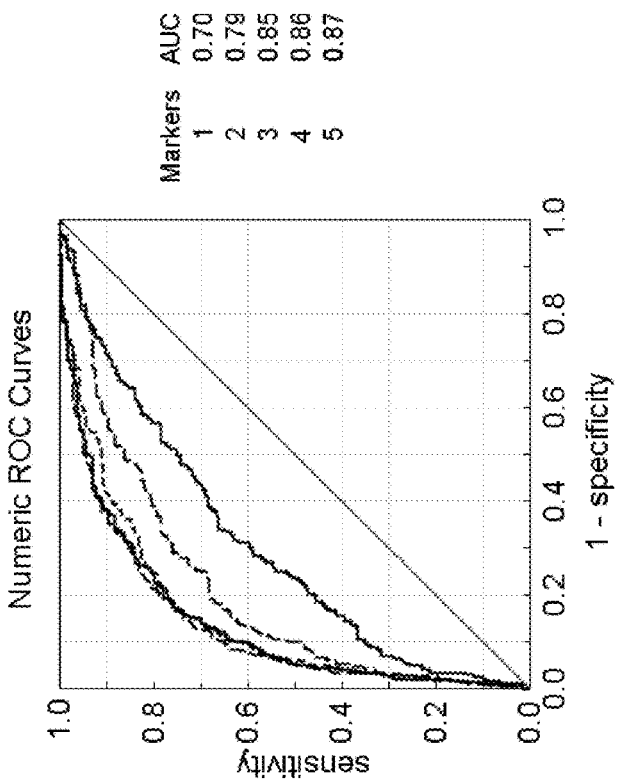
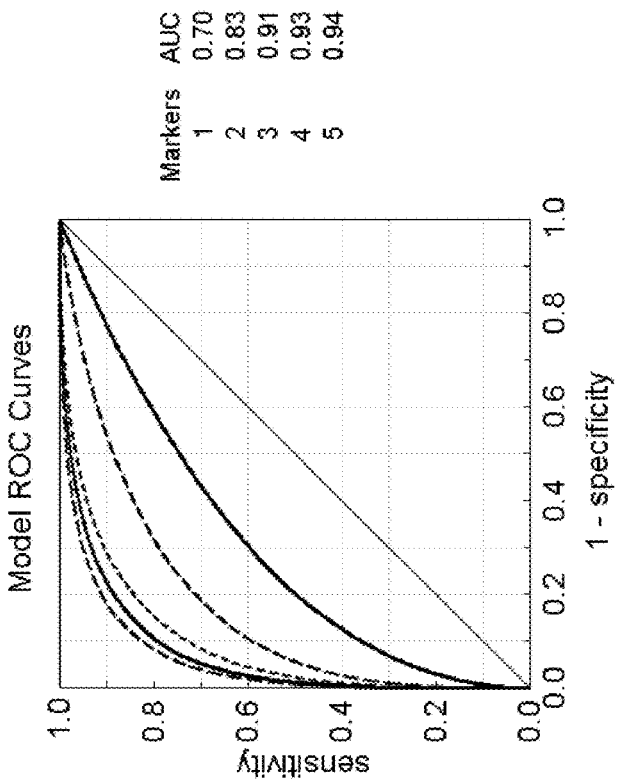


FIG 20A



LUNG CANCER BIOMARKERS AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Ser. No. 61/095,593, filed Sep. 9, 2008 and U.S. Provisional Application Ser. No. 61/152,837, filed Feb. 16, 2009, each of which is entitled "Multiplexed analyses of lung cancer samples", and each of which is incorporated herein by reference in its entirety for all purposes.

FIELD OF THE INVENTION

The present application relates generally to the detection of biomarkers and the diagnosis of cancer in an individual and, more specifically, to one or more biomarkers, methods, devices, reagents, systems, and kits for diagnosing cancer, more particularly lung cancer, in an individual.

BACKGROUND

The following description provides a summary of information relevant to the present application and is not an admission that any of the information provided or publications referenced herein is prior art to the present application.

More people die from lung cancer than any other type of cancer. This is true for both men and women. In 2005 in the United States (the most recent year for which statistics are currently available), lung cancer accounted for more deaths than breast cancer, prostate cancer, and colon cancer combined. In that year, 107,416 men and 89,271 women were diagnosed with lung cancer, and 90,139 men and 69,078 women died from lung cancer. Among men in the United States, lung cancer is the second most common cancer among white, black, Asian/Pacific Islander, American Indian/Alaska Native, and Hispanic men. Among women in the United States, lung cancer is the second most common cancer among white, black, and American Indian/Alaska Native women, and the third most common cancer among Asian/Pacific Islander and Hispanic women. For those who do not quit smoking, the probability of death from lung cancer is 15% and remains above 5% even for those who quit at age 50-59. The annual healthcare cost of lung cancer in the U.S. alone is $95 billion.

Ninety-one percent of lung cancer caused by smoking is non-small cell lung cancer (NSCLC), which represents approximately 87% of all lung cancers. The remaining 13% of all lung cancers are small cell lung cancers, although mixed-cell lung cancers do occur. Because small cell lung cancer is rare and rapidly fatal, the opportunity for early detection is small.

There are three main types of NSCLC: squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Adenocarcinoma is the most common form of lung cancer (30%-40% and reported to be as high as 50%) and is the lung cancer most frequently found in both smokers and non-smokers. Squamous cell carcinoma accounts for 25-30% of all lung cancers and is generally found in a proximal bronchus. Early stage NSCLC tends to be localized, and if detected early it can often be treated by surgery with a favorable outcome and improved survival. Other treatment options include radiation treatment, drug therapy, and a combination of these methods.

NSCLC is staged by the size of the tumor and its presence in other tissues including lymph nodes. In the occult stage, cancer cells are found in sputum samples or lavage samples and no tumor is detectable in the lungs. In stage 0, only the innermost lining of the lungs exhibit cancer cells and the tumor has not grown through the lining. In stage IA, the cancer is considered invasive and has grown deep into the lung tissue but the tumor is less than 3 cm across. In this stage, the tumor is not found in the bronchus or lymph nodes. In stage IB, the tumor is either larger than 3 cm across or has grown into the bronchus or pleura, but has not grown into the lymph nodes. In stage IIA, the tumor is more than 3 cm across and has grown into the lymph nodes. In stage IIB, the tumor has either been found in the lymph nodes and is greater than 3 cm across or grown into the bronchus or pleura; or the cancer is not in the lymph nodes but is found in the chest wall, diaphragm, pleura, bronchus, or tissue that surrounds the heart. In stage IIIA, cancer cells are found in the lymph nodes near the lung and bronchi and in those between the lungs but on the side of the chest where the tumor is located. Stage IIIB, cancer cells are located on the opposite side of the chest from the tumor and in the neck. Other organs near the lungs may also have cancer cells and multiple tumors may be found in one lobe of the lungs. In stage IV, tumors are found in more than one lobe of the same lung or both lungs and cancer cells are found in other parts of the body.

Current methods of diagnosis for lung cancer include testing sputum for cancerous cells, chest x-ray, fiber optic evaluation of airways, and low dose spiral computed tomography (CT). Sputum cytology has a very low sensitivity. Chest X-ray is also relatively insensitive, requiring lesions to be greater than 1 cm in size to be visible. Bronchoscopy requires that the tumor is visible inside airways accessible to the bronchoscope. The most widely recognized diagnostic method is CT, but in common with X-ray, the use of CT involves ionizing radiation, which itself can cause cancer. CT also has significant limitations: the scans require a high level of technical skill to interpret and many of the observed abnormalities are not in fact lung cancer and substantial healthcare costs are incurred in following up CT findings. The most common incidental finding is a benign lung nodule.

Lung nodules are relatively round lesions, or areas of abnormal tissue, located within the lung and may vary in size. Lung nodules may be benign or cancerous, but most are benign. If a nodule is below 4 mm the prevalence is only 1.5%, if 4-8 mm the prevalence is approximately 6%, and if above 20 mm the incidence is approximately 20%. For small and medium-sized nodules, the patient is advised to undergo a repeat scan within three months to a year. For many large nodules, the patient receives a biopsy (which is invasive and may lead to complications) even though most of these are benign.

Therefore, diagnostic methods that can replace or complement CT are needed to reduce the number of surgical procedures conducted and minimize the risk of surgical complications. In addition, even when lung nodules are absent or unknown, methods are needed to detect lung cancer at its early stages to improve patient outcomes. Only 16% of lung cancer cases are diagnosed as localized, early stage cancer, where the 5-year survival rate is 46%, compared to 84% of those diagnosed at late stage, where the 5-year survival rate is only 13%. This demonstrates that relying on symptoms for diagnosis is not useful because many of them are common to other lung disease. These symptoms include a persistent cough, bloody sputum, chest pain, and recurring bronchitis or pneumonia.

Where methods of early diagnosis in cancer exist, the benefits are generally accepted by the medical community.

Cancers that have widely utilized screening protocols have the highest 5-year survival rates, such as breast cancer (88%) and colon cancer (65%) versus 16% for lung cancer. However, 88% of lung cancer patients survive ten years or longer if the cancer is diagnosed at Stage 1 through screening. This demonstrates the clear need for diagnostic methods that can reliably detect early-stage NSCLC.

Biomarker selection for a specific disease state involves first the identification of markers that have a measurable and statistically significant difference in a disease population compared to a control population for a specific medical application. Biomarkers can include secreted or shed molecules that parallel disease development or progression and readily diffuse into the blood stream from lung tissue or from distal tissues in response to a lesion. The biomarker or set of biomarkers identified are generally clinically validated or shown to be a reliable indicator for the original intended use for which it was selected. Biomarkers can include small molecules, peptides, proteins, and nucleic acids. Some of the key issues that affect the identification of biomarkers include over-fitting of the available data and bias in the data.

A variety of methods have been utilized in an attempt to identify biomarkers and diagnose disease. For protein-based markers, these include two-dimensional electrophoresis, mass spectrometry, and immunoassay methods. For nucleic acid markers, these include mRNA expression profiles, microRNA profiles, FISH, serial analysis of gene expression (SAGE), and large scale gene expression arrays.

The utility of two-dimensional electrophoresis is limited by low detection sensitivity; issues with protein solubility, charge, and hydrophobicity; gel reproducibility; and the possibility of a single spot representing multiple proteins. For mass spectrometry, depending on the format used, limitations revolve around the sample processing and separation, sensitivity to low abundance proteins, signal to noise considerations, and inability to immediately identify the detected protein. Limitations in immunoassay approaches to biomarker discovery are centered on the inability of antibody-based multiplex assays to measure a large number of analytes. One might simply print an array of high-quality antibodies and, without sandwiches, measure the analytes bound to those antibodies. (This would be the formal equivalent of using a whole genome of nucleic acid sequences to measure by hybridization all DNA or RNA sequences in an organism or a cell. The hybridization experiment works because hybridization can be a stringent test for identity. Even very good antibodies are not stringent enough in selecting their binding partners to work in the context of blood or even cell extracts because the protein ensemble in those matrices have extremely different abundances.) Thus, one must use a different approach with immunoassay-based approaches to biomarker discovery—one would need to use multiplexed ELISA assays (that is, sandwiches) to get sufficient stringency to measure many analytes simultaneously to decide which analytes are indeed biomarkers. Sandwich immunoassays do not scale to high content, and thus biomarker discovery using stringent sandwich immunoassays is not possible using standard array formats. Lastly, antibody reagents are subject to substantial lot variability and reagent instability. The instant platform for protein biomarker discovery overcomes this problem.

Many of these methods rely on or require some type of sample fractionation prior to the analysis. Thus the sample preparation required to run a sufficiently powered study designed to identify/discover statistically relevant biomarkers in a series of well-defined sample populations is extremely difficult, costly, and time consuming During fractionation, a wide range of variability can be introduced into the various samples. For example, a potential marker could be unstable to the process, the concentration of the marker could be changed, inappropriate aggregation or disaggregation could occur, and inadvertent sample contamination could occur and thus obscure the subtle changes anticipated in early disease.

It is widely accepted that biomarker discovery and detection methods using these technologies have serious limitations for the identification of diagnostic biomarkers. These limitations include an inability to detect low-abundance biomarkers, an inability to consistently cover the entire dynamic range of the proteome, irreproducibility in sample processing and fractionation, and overall irreproducibility and lack of robustness of the method. Further, these studies have introduced biases into the data and not adequately addressed the complexity of the sample populations, including appropriate controls, in terms of the distribution and randomization required to identify and validate biomarkers within a target disease population.

Although efforts aimed at the discovery of new and effective biomarkers have gone on for several decades, the efforts have been largely unsuccessful. Biomarkers for various diseases typically have been identified in academic laboratories, usually through an accidental discovery while doing basic research on some disease process. Based on the discovery and with small amounts of clinical data, papers were published that suggested the identification of a new biomarker. Most of these proposed biomarkers, however, have not been confirmed as real or useful biomarkers, primarily because the small number of clinical samples tested provide only weak statistical proof that an effective biomarker has in fact been found. That is, the initial identification was not rigorous with respect to the basic elements of statistics. In each of the years 1994 through 2003, a search of the scientific literature shows that thousands of references directed to biomarkers were published. During that same time frame, however, the FDA approved for diagnostic use, at most, three new protein biomarkers a year, and in several years no new protein biomarkers were approved.

Based on the history of failed biomarker discovery efforts, mathematical theories have been proposed that further promote the general understanding that biomarkers for disease are rare and difficult to find. Biomarker research based on 2D gels or mass spectrometry supports these notions. Very few useful biomarkers have been identified through these approaches. However, it is usually overlooked that 2D gel and mass spectrometry measure proteins that are present in blood at approximately 1 nM concentrations and higher, and that this ensemble of proteins may well be the least likely to change with disease. Other than the instant biomarker discovery platform, proteomic biomarker discovery platforms that are able to accurately measure protein expression levels at much lower concentrations do not exist.

Much is known about biochemical pathways for complex human biology. Many biochemical pathways culminate in or are started by secreted proteins that work locally within the pathology, for example growth factors are secreted to stimulate the replication of other cells in the pathology, and other factors are secreted to ward off the immune system, and so on. While many of these secreted proteins work in a paracrine fashion, some operate distally in the body. One skilled in the art with a basic understanding of biochemical pathways would understand that many pathology-specific proteins ought to exist in blood at concentrations below (even far below) the detection limits of 2D gels and mass spectrometry. What must precede the identification of this rela-

tively abundant number of disease biomarkers is a proteomic platform that can analyze proteins at concentrations below those detectable by 2D gels or mass spectrometry.

Accordingly, a need exists for biomarkers, methods, devices, reagents, systems, and kits that enable (a) the differentiation of benign pulmonary nodules from malignant pulmonary nodules; (b) the detection of lung cancer biomarkers; and (c) the diagnosis of lung cancer.

SUMMARY

The present application includes biomarkers, methods, reagents, devices, systems, and kits for the detection and diagnosis of cancer and more particularly, lung cancer. The biomarkers of the present application were identified using a multiplex aptamer-based assay which is described in detail in Example 1. By using the aptamer-based biomarker identification method described herein, this application describes a surprisingly large number of lung cancer biomarkers that are useful for the detection and diagnosis of lung cancer. In identifying these biomarkers, over 800 proteins from hundreds of individual samples were measured, some of which were at concentrations in the low femtomolar range. This is about four orders of magnitude lower than biomarker discovery experiments done with 2D gels and/or mass spectrometry.

While certain of the described lung cancer biomarkers are useful alone for detecting and diagnosing lung cancer, methods are described herein for the grouping of multiple subsets of the lung cancer biomarkers that are useful as a panel of biomarkers. Once an individual biomarker or subset of biomarkers has been identified, the detection or diagnosis of lung cancer in an individual can be accomplished using any assay platform or format that is capable of measuring differences in the levels of the selected biomarker or biomarkers in a biological sample.

However, it was only by using the aptamer-based biomarker identification method described herein, wherein over 800 separate potential biomarker values were individually screened from a large number of individuals having previously been diagnosed either as having or not having lung cancer that it was possible to identify the lung cancer biomarkers disclosed herein. This discovery approach is in stark contrast to biomarker discovery from conditioned media or lysed cells as it queries a more patient-relevant system that requires no translation to human pathology.

Thus, in one aspect of the instant application, one or more biomarkers are provided for use either alone or in various combinations to diagnose lung cancer or permit the differential diagnosis of pulmonary nodules as benign or malignant. Exemplary embodiments include the biomarkers provided in Table 1, Col. 2, which as noted above, were identified using a multiplex aptamer-based assay, as described generally in Example 1 and more specifically in Example 2. The markers provided in Table 1, Col. 5 are useful in distinguishing benign nodules from cancerous nodules. The markers provided in Table 1, Col. 6 are useful in distinguishing asymptomatic smokers from smokers having lung cancer.

While certain of the described lung cancer biomarkers are useful alone for detecting and diagnosing lung cancer, methods are also described herein for the grouping of multiple subsets of the lung cancer biomarkers that are each useful as a panel of three or more biomarkers. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least two biomarkers. In other embodiments, N is selected to be any number from 2-61 biomarkers.

In yet other embodiments, N is selected to be any number from 2-7, 2-10, 2-15, 2-20, 2-25, 2-30, 2-35, 2-40, 2-45, 2-50, 2-55, or 2-61. In other embodiments, N is selected to be any number from 3-7, 3-10, 3-15, 3-20, 3-25, 3-30, 3-35, 3-40, 3-45, 3-50, 3-55, or 3-61. In other embodiments, N is selected to be any number from 4-7, 4-10, 4-15, 4-20, 4-25, 4-30, 4-35, 4-40, 4-45, 4-50, 4-55, or 4-61. In other embodiments, N is selected to be any number from 5-7, 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, 5-45, 5-50, 5-55, or 5-61. In other embodiments, N is selected to be any number from 6-10, 6-15, 6-20, 6-25, 6-30, 6-35, 6-40, 6-45, 6-50, 6-55, or 6-61. In other embodiments, N is selected to be any number from 7-10, 7-15, 7-20, 7-25, 7-30, 7-35, 7-40, 7-45, 7-50, 7-55, or 7-61. In other embodiments, N is selected to be any number from 8-10, 8-15, 8-20, 8-25, 8-30, 8-35, 8-40, 8-45, 8-50, 8-55, or 8-61. In other embodiments, N is selected to be any number from 9-15, 9-20, 9-25, 9-30, 9-35, 9-40, 9-45, 9-50, 9-55, or 9-61. In other embodiments, N is selected to be any number from 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-45, 10-50, 10-55, or 10-61. It will be appreciated that N can be selected to encompass similar, but higher order, ranges.

In another aspect, a method is provided for diagnosing lung cancer in an individual, the method including detecting, in a biological sample from an individual, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers provided in Table 1, Col. 2, wherein the individual is classified as having lung cancer based on the at least one biomarker value.

In another aspect, a method is provided for diagnosing lung cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, Col. 2, wherein the likelihood of the individual having lung cancer is determined based on the biomarker values.

In another aspect, a method is provided for diagnosing lung cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, Col. 2, wherein the individual is classified as having lung cancer based on the biomarker values, and wherein N=2-10.

In another aspect, a method is provided for diagnosing lung cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, Col. 2, wherein the likelihood of the individual having lung cancer is determined based on the biomarker values, and wherein N=2-10.

In another aspect, a method is provided for differentiating an individual having a benign nodule from an individual having a malignant nodule, the method including detecting, in a biological sample from an individual, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers set forth in Table 1, Col. 5, wherein the individual is classified as having a malignant nodule, or the likelihood of the individual having a malignant nodule is determined, based on the at least one biomarker value.

In another aspect, a method is provided for differentiating an individual having a benign nodule from an individual having a malignant nodule, the method including detecting, in a biological sample from an individual, biomarker values

that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, Col. 5, wherein the individual is classified as having a malignant nodule, or the likelihood of the individual having a malignant nodule is determined, based on said biomarker values, wherein N=2-10.

In another aspect, a method is provided for screening smokers for lung cancer, the method including detecting, in a biological sample from an individual who is a smoker, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers set forth in Table 1, Col. 6, wherein the individual is classified as having lung cancer, or the likelihood of the individual having lung cancer is determined, based on the at least one biomarker value.

In another aspect, a method is provided for screening smokers for lung cancer, the method including detecting, in a biological sample from an individual who is a smoker, biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, Col. 6, wherein the individual is classified as having lung cancer, or the likelihood of the individual having lung cancer is determined, based on said biomarker values, wherein N=2-10.

In another aspect, a method is provided for diagnosing that an individual does not have lung cancer, the method including detecting, in a biological sample from an individual, at least one biomarker value corresponding to at least one biomarker selected from the group of biomarkers set forth in Table 1, Col. 2, wherein the individual is classified as not having lung cancer based on the at least one biomarker value.

In another aspect, a method is provided for diagnosing that an individual does not have lung cancer, the method including detecting, in a biological sample from an individual, biomarker values that each corresponding to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, Col. 2, wherein the individual is classified as not having lung cancer based on the biomarker values, and wherein N=2-10.

In another aspect, a method is provided for diagnosing lung cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 2, wherein a classification of the biomarker values indicates that the individual has lung cancer, and wherein N=3-10.

In another aspect, a method is provided for diagnosing lung cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 2, wherein a classification of the biomarker values indicates that the individual has lung cancer, and wherein N=3-15.

In another aspect, a method is provided for diagnosing lung cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of biomarkers selected from the group of panels set forth in Tables 2-27, wherein a classification of the biomarker values indicates that the individual has lung cancer.

In another aspect, a method is provided for differentiating an individual having a benign nodule from an individual having a malignant nodule, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 5, wherein the individual is classified as having a malignant nodule, or the likelihood of the individual having a malignant nodule is determined, based on the biomarker values, and wherein N=3-10.

In another aspect, a method is provided for differentiating an individual having a benign nodule from an individual having a malignant nodule, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 5, wherein the individual is classified as having a malignant nodule, or the likelihood of the individual having a malignant nodule is determined, based on the biomarker values, and wherein N=3-15.

In another aspect, a method is provided for screening smokers for lung cancer, the method including detecting, in a biological sample from an individual who is a smoker, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 6, wherein the individual is classified as having lung cancer, or the likelihood of the individual having lung cancer is determined, based on the biomarker values, and wherein N=3-10.

In another aspect, a method is provided for screening smokers for lung cancer, the method including detecting, in a biological sample from an individual who is a smoker, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 6, wherein the individual is classified as having lung cancer, or the likelihood of the individual having lung cancer is determined, based on the biomarker values, wherein N=3-15.

In another aspect, a method is provided for diagnosing an absence of lung cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 2, wherein a classification of the biomarker values indicates an absence of lung cancer in the individual, and wherein N=3-10.

In another aspect, a method is provided for diagnosing an absence of lung cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 2, wherein a classification of the biomarker values indicates an absence of lung cancer in the individual, and wherein N=3-15.

In another aspect, a method is provided for diagnosing an absence of lung cancer, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of biomarkers selected from the group of panels provided in Tables 2-27, wherein a classification of the biomarker values indicates an absence of lung cancer in the individual.

In another aspect, a method is provided for diagnosing lung cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, Col. 2, wherein the individual is classified as having lung cancer based on a classification score that deviates from a predetermined threshold, and wherein N=2-10.

In another aspect, a method is provided for differentiating an individual having a benign nodule from an individual having a malignant nodule, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 5, wherein the individual is classified as having a malignant nodule, or the likelihood of the individual having a malignant nodule is determined, based on a classification score that deviates from a predetermined threshold, and wherein N=3-10.

In another aspect, a method is provided for differentiating an individual having a benign nodule from an individual having a malignant nodule, the method including detecting, in a biological sample from an individual, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 5, wherein the individual is classified as having a malignant nodule, or the likelihood of the individual having a malignant nodule is determined, based on a classification score that deviates from a predetermined threshold, wherein N=3-15.

In another aspect, a method is provided for screening smokers for lung cancer, the method including detecting, in a biological sample from an individual who is a smoker, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 6, wherein the individual is classified as having lung cancer, or the likelihood of the individual having lung cancer is determined, based on a classification score that deviates from a predetermined threshold, wherein N=3-10.

In another aspect, a method is provided for screening smokers for lung cancer, the method including detecting, in a biological sample from an individual who is a smoker, biomarker values that each correspond to a biomarker on a panel of N biomarkers, wherein the biomarkers are selected from the group of biomarkers set forth in Table 1, Col. 6, wherein the individual is classified as having lung cancer, or the likelihood of the individual having lung cancer is determined, based on a classification score that deviates from a predetermined threshold, wherein N=3-15.

In another aspect, a method is provided for diagnosing an absence of lung cancer in an individual, the method including detecting, in a biological sample from an individual, biomarker values that correspond to one of at least N biomarkers selected from the group of biomarkers set forth in Table 1, Col. 2, wherein said individual is classified as not having lung cancer based on a classification score that deviates from a predetermined threshold, and wherein N=2-10.

In another aspect, a computer-implemented method is provided for indicating a likelihood of lung cancer. The method comprises: retrieving on a computer biomarker information for an individual, wherein the biomarker information comprises biomarker values that each correspond to one of at least N biomarkers, wherein N is as defined above, selected from the group of biomarkers set forth in Table 1, Col. 2; performing with the computer a classification of each of the biomarker values; and indicating a likelihood that the individual has lung cancer based upon a plurality of classifications.

In another aspect, a computer-implemented method is provided for classifying an individual as either having or not having lung cancer. The method comprises: retrieving on a computer biomarker information for an individual, wherein the biomarker information comprises biomarker values that each correspond to one of at least N biomarkers selected from the group of biomarkers provided in Table 1, Col. 2; performing with the computer a classification of each of the biomarker values; and indicating whether the individual has lung cancer based upon a plurality of classifications.

In another aspect, a computer program product is provided for indicating a likelihood of lung cancer. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises biomarker values that each correspond to one of at least N biomarkers, wherein N is as defined above, in the biological sample selected from the group of biomarkers set forth in Table 1, Col. 2; and code that executes a classification method that indicates a likelihood that the individual has lung cancer as a function of the biomarker values.

In another aspect, a computer program product is provided for indicating a lung cancer status of an individual. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises biomarker values that each correspond to one of at least N biomarkers in the biological sample selected from the group of biomarkers provided in Table 1, Col. 2; and code that executes a classification method that indicates a lung cancer status of the individual as a function of the biomarker values.

In another aspect, a computer-implemented method is provided for indicating a likelihood of lung cancer. The method comprises retrieving on a computer biomarker information for an individual, wherein the biomarker information comprises a biomarker value corresponding to a biomarker selected from the group of biomarkers set forth in Table 1, Col. 2; performing with the computer a classification of the biomarker value; and indicating a likelihood that the individual has lung cancer based upon the classification.

In another aspect, a computer-implemented method is provided for classifying an individual as either having or not having lung cancer. The method comprises retrieving from a computer biomarker information for an individual, wherein the biomarker information comprises a biomarker value corresponding to a biomarker selected from the group of biomarkers provided in Table 1, Col. 2; performing with the computer a classification of the biomarker value; and indicating whether the individual has lung cancer based upon the classification.

In still another aspect, a computer program product is provided for indicating a likelihood of lung cancer. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises a biomarker value corresponding to a biomarker in the biological sample selected from the group of biomarkers set forth in Table 1, Col. 2; and code that executes a classification method that indicates a likelihood that the individual has lung cancer as a function of the biomarker value.

In still another aspect, a computer program product is provided for indicating a lung cancer status of an individual. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program

code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises a biomarker value corresponding to a biomarker in the biological sample selected from the group of biomarkers provided in Table 1, Col. 2; and code that executes a classification method that indicates a lung cancer status of the individual as a function of the biomarker value.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A is a flowchart for an exemplary method for detecting lung cancer in a biological sample.

FIG. **1**B is a flowchart for an exemplary method for detecting lung cancer in a biological sample using a naïve Bayes classification method.

FIG. **2** shows a ROC curve for a single biomarker, SCFsR, using a naïve Bayes classifier for a test that detects lung cancer in asymptomatic smokers.

FIG. **3** shows ROC curves for biomarker panels of from one to ten biomarkers using naïve Bayes classifiers for a test that detects lung cancer in asymptomatic smokers.

FIG. **4** illustrates the increase in the classification score (specificity+sensitivity) as the number of biomarkers is increased from one to ten using naïve Bayes classification for a benign nodule-lung cancer panel.

FIG. **5** shows the measured biomarker distributions for SCFsR as a cumulative distribution function (cdf) in log-transformed RFU for the benign nodule control group (solid line) and the lung cancer disease group (dotted line) along with their curve fits to a normal cdf (dashed lines) used to train the naïve Bayes classifiers.

FIG. **6** illustrates an exemplary computer system for use with various computer-implemented methods described herein.

FIG. **7** is a flowchart for a method of indicating the likelihood that an individual has lung cancer in accordance with one embodiment.

FIG. **8** is a flowchart for a method of indicating the likelihood that an individual has lung cancer in accordance with one embodiment.

FIG. **9** illustrates an exemplary aptamer assay that can be used to detect one or more lung cancer biomarkers in a biological sample.

FIG. **10** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between NSCLC and benign nodules from an aggregated set of potential biomarkers.

FIG. **11** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between NSCLC and asymptomatic smokers from an aggregated set of potential biomarkers.

FIG. **12** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between NSCLC and benign nodules from a site-consistent set of potential biomarkers.

FIG. **13** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between NSCLC and asymptomatic smokers from a site-consistent set of potential biomarkers.

FIG. **14** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between NSCLC and benign nodules from a set of potential biomarkers resulting from a combination of aggregated and site-consistent markers.

FIG. **15** shows a histogram of frequencies for which biomarkers were used in building classifiers to distinguish between NSCLC and asymptomatic smokers from a set of potential biomarkers resulting from a combination of aggregated and site-consistent markers.

FIG. **16** shows gel images resulting from pull-down experiments that illustrate the specificity of aptamers as capture reagents for the proteins LBP, C9 and IgM. For each gel, lane 1 is the eluate from the Streptavidin-agarose beads, lane 2 is the final eluate, and lane is a MW marker lane (major bands are at 110, 50, 30, 15, and 3.5 kDa from top to bottom).

FIG. **17**A shows a pair of histograms summarizing all possible single protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1, Col 5 (solid) and a set of random markers (dotted).

FIG. **17**B shows a pair of histograms summarizing all possible two-protein protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1, Col 5 (solid) and a set of random markers (dotted).

FIG. **17**C shows a pair of histograms summarizing all possible three-protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1, Col 5 (solid) and a set of random markers (dotted).

FIG. **18**A shows a pair of histograms summarizing all possible single protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1, Col 6 (solid) and a set of random markers (dotted).

FIG. **18**B shows a pair of histograms summarizing all possible two-protein protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1, Col 6 (solid) and a set of random markers (dotted).

FIG. **18**C shows a pair of histograms summarizing all possible three-protein naïve Bayes classifier scores (sensitivity+specificity) using the biomarkers set forth in Table 1, Col 6 (solid) and a set of random markers (dotted).

FIG. **19**A shows the sensitivity+specificity score for naïve Bayes classifiers using from 2-10 markers selected from the full panel (♦) and the scores obtained by dropping the best 5 (■), 10 (▲) and 15 (x) markers during classifier generation for the benign nodule control group.

FIG. **19**B shows the sensitivity+specificity score for naïve Bayes classifiers using from 2-10 markers selected from the full panel (♦) and the scores obtained by dropping the best 5 (■), 10 (▲) and 15 (x) markers during classifier generation for the smoker control group.

FIG. **20**A shows a set of ROC curves modeled from the data in Tables 38 and 39 for panels of from one to five markers.

FIG. **20**B shows a set of ROC curves computed from the training data for panels of from one to five markers as in FIG. **19**A.

DETAILED DESCRIPTION

Reference will now be made in detail to representative embodiments of the invention. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that the invention is not intended to be limited to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents that may be included within the scope of the present invention as defined by the claims.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in and are within the scope of the practice of the present invention. The present invention is in no way limited to the methods and materials described.

Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly under-

stood by one of ordinary skill in the art to which this invention belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

All publications, published patent documents, and patent applications cited in this application are indicative of the level of skill in the art(s) to which the application pertains. All publications, published patent documents, and patent applications cited herein are hereby incorporated by reference to the same extent as though each individual publication, published patent document, or patent application was specifically and individually indicated as being incorporated by reference.

As used in this application, including the appended claims, the singular forms "a," "an," and "the" include plural references, unless the content clearly dictates otherwise, and are used interchangeably with "at least one" and "one or more." Thus, reference to "an aptamer" includes mixtures of aptamers, reference to "a probe" includes mixtures of probes, and the like.

As used herein, the term "about" represents an insignificant modification or variation of the numerical value such that the basic function of the item to which the numerical value relates is unchanged.

As used herein, the terms "comprises," "comprising," "includes," "including," "contains," "containing," and any variations thereof, are intended to cover a non-exclusive inclusion, such that a process, method, product-by-process, or composition of matter that comprises, includes, or contains an element or list of elements does not include only those elements but may include other elements not expressly listed or inherent to such process, method, product-by-process, or composition of matter.

The present application includes biomarkers, methods, devices, reagents, systems, and kits for the detection and diagnosis of lung cancer.

In one aspect, one or more biomarkers are provided for use either alone or in various combinations to diagnose lung cancer, permit the differential diagnosis of pulmonary nodules as benign or malignant, monitor lung cancer recurrence, or address other clinical indications. As described in detail below, exemplary embodiments include the biomarkers provided in Table 1, Col. 2, which were identified using a multiplex aptamer-based assay that is described generally in Example 1 and more specifically in Example 2.

Table 1, Col. 2 sets forth the findings obtained from analyzing hundreds of individual blood samples from NSCLC cancer cases, and hundreds of equivalent individual blood samples from smokers and from individuals diagnosed with benign lung nodules. The smoker and benign nodule groups were designed to match the populations with which a lung cancer diagnostic test can have the most benefit. (These cases and controls were obtained from multiple clinical sites to mimic the range of real world conditions under which such a test can be applied). The potential biomarkers were measured in individual samples rather than pooling the disease and control blood; this allowed a better understanding of the individual and group variations in the phenotypes associated with the presence and absence of disease (in this case lung cancer). Since over 800 protein measurements were made on each sample, and several hundred samples from each of the disease and the control populations were individually measured, Table 1, Col. 2 resulted from an analysis of an uncommonly large set of data. The measurements were analyzed using the methods described in the section, "Classification of Biomarkers and Calculation of Disease Scores" herein.

Table 1, Col. 2 lists the biomarkers found to be useful in distinguishing samples obtained from individuals with NSCLC from "control" samples obtained from smokers and individuals with benign lung nodules. Using a multiplex aptamer assay as described herein, thirty-eight biomarkers were discovered that distinguished the samples obtained from individuals who had lung cancer from the samples obtained from individuals in the smoker control group (see Table 1, Col. 6). Similarly, using a multiplex aptamer assay, forty biomarkers were discovered that distinguished samples obtained from individuals with NSCLC from samples obtained from people who had benign lung nodules (see Table 1, Col. 5). Together, the two lists of 38 and 40 biomarkers are comprised of 61 unique biomarkers, because there is considerable overlap between the list of biomarkers for distinguishing NSCLC from benign nodules and the list for distinguishing NSCLC from smokers who do not have lung cancer.

While certain of the described lung cancer biomarkers are useful alone for detecting and diagnosing lung cancer, methods are also described herein for the grouping of multiple subsets of the lung cancer biomarkers, where each grouping or subset selection is useful as a panel of three or more biomarkers, interchangeably referred to herein as a "biomarker panel" and a panel. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least two biomarkers. In other embodiments, N is selected from 2-61 biomarkers.

In yet other embodiments, N is selected to be any number from 2-7, 2-10, 2-15, 2-20, 2-25, 2-30, 2-35, 2-40, 2-45, 2-50, 2-55, or 2-61. In other embodiments, N is selected to be any number from 3-7, 3-10, 3-15, 3-20, 3-25, 3-30, 3-35, 3-40, 3-45, 3-50, 3-55, or 3-61. In other embodiments, N is selected to be any number from 4-7, 4-10, 4-15, 4-20, 4-25, 4-30, 4-35, 4-40, 4-45, 4-50, 4-55, or 4-61. In other embodiments, N is selected to be any number from 5-7, 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, 5-45, 5-50, 5-55, or 5-61. In other embodiments, N is selected to be any number from 6-10, 6-15, 6-20, 6-25, 6-30, 6-35, 6-40, 6-45, 6-50, 6-55, or 6-61. In other embodiments, N is selected to be any number from 7-10, 7-15, 7-20, 7-25, 7-30, 7-35, 7-40, 7-45, 7-50, 7-55, or 7-61. In other embodiments, N is selected to be any number from 8-10, 8-15, 8-20, 8-25, 8-30, 8-35, 8-40, 8-45, 8-50, 8-55, or 8-61. In other embodiments, N is selected to be any number from 9-15, 9-20, 9-25, 9-30, 9-35, 9-40, 9-45, 9-50, 9-55, or 9-61. In other embodiments, N is selected to be any number from 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-45, 10-50, 10-55, or 10-61. It will be appreciated that N can be selected to encompass similar, but higher order, ranges.

In one embodiment, the number of biomarkers useful for a biomarker subset or panel is based on the sensitivity and specificity value for the particular combination of biomarker values. The terms "sensitivity" and "specificity" are used herein with respect to the ability to correctly classify an individual, based on one or more biomarker values detected in their biological sample, as having lung cancer or not having lung cancer. "Sensitivity" indicates the performance of the biomarker(s) with respect to correctly classifying individuals that have lung cancer. "Specificity" indicates the performance of the biomarker(s) with respect to correctly classifying individuals who do not have lung cancer. For example, 85% specificity and 90% sensitivity for a panel of markers used to test a set of control samples and lung cancer samples indicates that 85% of the control samples were

correctly classified as control samples by the panel, and 90% of the lung cancer samples were correctly classified as lung cancer samples by the panel. The desired or preferred minimum value can be determined as described in Example 3. Representative panels are set forth in Tables 2-27, which set forth a series of 100 different panels of 3-15 biomarkers, which have the indicated levels of specificity and sensitivity for each panel. The total number of occurrences of each marker in each of these panels is indicated at the bottom of each Table.

In one aspect, lung cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to at least one of the biomarkers ERBB1, LRIG3 or SCFsR and at least N additional biomarkers selected from the list of biomarkers in Table 1, Col. 2, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15. In a further aspect, lung cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarkers ERBB1, LRIG3 and SCFsR and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, Col. 2, wherein N equals 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13. In a further aspect, lung cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker ERBB1 and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, Col. 2, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15. In a further aspect, lung cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker LRIG3 and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, Col. 2, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15. In a further aspect, lung cancer is detected or diagnosed in an individual by conducting an assay on a biological sample from the individual and detecting biomarker values that each correspond to the biomarker SCFsR and one of at least N additional biomarkers selected from the list of biomarkers in Table 1, Col. 2, wherein N equals 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

The lung cancer biomarkers identified herein represent a relatively large number of choices for subsets or panels of biomarkers that can be used to effectively detect or diagnose lung cancer. Selection of the desired number of such biomarkers depends on the specific combination of biomarkers chosen. It is important to remember that panels of biomarkers for detecting or diagnosing lung cancer may also include biomarkers not found in Table 1, Col. 2, and that the inclusion of additional biomarkers not found in Table 1, Col. 2 may reduce the number of biomarkers in the particular subset or panel that is selected from Table 1, Col. 2. The number of biomarkers from Table 1, Col. 2 used in a subset or panel may also be reduced if additional biomedical information is used in conjunction with the biomarker values to establish acceptable sensitivity and specificity values for a given assay.

Another factor that can affect the number of biomarkers to be used in a subset or panel of biomarkers is the procedures used to obtain biological samples from individuals who are being diagnosed for lung cancer. In a carefully controlled sample procurement environment, the number of biomarkers necessary to meet desired sensitivity and specificity values will be lower than in a situation where there can be more variation in sample collection, handling and storage. In developing the list of biomarkers set forth in Table 1, Col. 2, multiple sample collection sites were utilized to collect data for classifier training. This provides for more robust biomarkers that are less sensitive to variations in sample collection, handling and storage, but can also require that the number of biomarkers in a subset or panel be larger than if the training data were all obtained under very similar conditions.

One aspect of the instant application can be described generally with reference to FIGS. **1**A and B. A biological sample is obtained from an individual or individuals of interest. The biological sample is then assayed to detect the presence of one or more (N) biomarkers of interest and to determine a biomarker value for each of said N biomarkers (referred to in FIG. **1**B as marker RFU). Once a biomarker has been detected and a biomarker value assigned each marker is scored or classified as described in detail herein. The marker scores are then combined to provide a total diagnostic score, which indicates the likelihood that the individual from whom the sample was obtained has lung cancer.

As used herein, "lung" may be interchangeably referred to as "pulmonary".

As used herein, "smoker" refers to an individual who has a history of tobacco smoke inhalation.

"Biological sample", "sample", and "test sample" are used interchangeably herein to refer to any material, biological fluid, tissue, or cell obtained or otherwise derived from an individual. This includes blood (including whole blood, leukocytes, peripheral blood mononuclear cells, buffy coat, plasma, and serum), sputum, tears, mucus, nasal washes, nasal aspirate, breath, urine, semen, saliva, meningeal fluid, amniotic fluid, glandular fluid, lymph fluid, nipple aspirate, bronchial aspirate, synovial fluid, joint aspirate, cells, a cellular extract, and cerebrospinal fluid. This also includes experimentally separated fractions of all of the preceding. For example, a blood sample can be fractionated into serum or into fractions containing particular types of blood cells, such as red blood cells or white blood cells (leukocytes). If desired, a sample can be a combination of samples from an individual, such as a combination of a tissue and fluid sample. The term "biological sample" also includes materials containing homogenized solid material, such as from a stool sample, a tissue sample, or a tissue biopsy, for example. The term "biological sample" also includes materials derived from a tissue culture or a cell culture. Any suitable methods for obtaining a biological sample can be employed; exemplary methods include, e.g., phlebotomy, swab (e.g., buccal swab), and a fine needle aspirate biopsy procedure. Exemplary tissues susceptible to fine needle aspiration include lymph node, lung, lung washes, BAL (bronchoalveolar lavage), thyroid, breast, and liver. Samples can also be collected, e.g., by micro dissection (e.g., laser capture micro dissection (LCM) or laser micro dissection (LMD)), bladder wash, smear (e.g., a PAP smear), or ductal lavage. A "biological sample" obtained or derived from an individual includes any such sample that has been processed in any suitable manner after being obtained from the individual.

Further, it should be realized that a biological sample can be derived by taking biological samples from a number of individuals and pooling them or pooling an aliquot of each individual's biological sample. The pooled sample can be treated as a sample from a single individual and if the presence of cancer is established in the pooled sample, then

each individual biological sample can be re-tested to determine which individual/s have lung cancer.

For purposes of this specification, the phrase "data attributed to a biological sample from an individual" is intended to mean that the data in some form derived from, or were generated using, the biological sample of the individual. The data may have been reformatted, revised, or mathematically altered to some degree after having been generated, such as by conversion from units in one measurement system to units in another measurement system; but, the data are understood to have been derived from, or were generated using, the biological sample.

"Target", "target molecule", and "analyte" are used interchangeably herein to refer to any molecule of interest that may be present in a biological sample. A "molecule of interest" includes any minor variation of a particular molecule, such as, in the case of a protein, for example, minor variations in amino acid sequence, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component, which does not substantially alter the identity of the molecule. A "target molecule", "target", or "analyte" is a set of copies of one type or species of molecule or multi-molecular structure. "Target molecules", "targets", and "analytes" refer to more than one such set of molecules. Exemplary target molecules include proteins, polypeptides, nucleic acids, carbohydrates, lipids, polysaccharides, glycoproteins, hormones, receptors, antigens, antibodies, affybodies, antibody mimics, viruses, pathogens, toxic substances, substrates, metabolites, transition state analogs, cofactors, inhibitors, drugs, dyes, nutrients, growth factors, cells, tissues, and any fragment or portion of any of the foregoing.

As used herein, "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. Polypeptides can be single chains or associated chains. Also included within the definition are preproteins and intact mature proteins; peptides or polypeptides derived from a mature protein; fragments of a protein; splice variants; recombinant forms of a protein; protein variants with amino acid modifications, deletions, or substitutions; digests; and post-translational modifications, such as glycosylation, acetylation, phosphorylation, and the like.

As used herein, "marker" and "biomarker" are used interchangeably to refer to a target molecule that indicates or is a sign of a normal or abnormal process in an individual or of a disease or other condition in an individual. More specifically, a "marker" or "biomarker" is an anatomic, physiologic, biochemical, or molecular parameter associated with the presence of a specific physiological state or process, whether normal or abnormal, and, if abnormal, whether chronic or acute. Biomarkers are detectable and measurable by a variety of methods including laboratory assays and medical imaging. When a biomarker is a protein, it is also possible to use the expression of the corresponding gene as a surrogate measure of the amount or presence or absence of the corresponding protein biomarker in a biological sample or methylation state of the gene encoding the biomarker or proteins that control expression of the biomarker.

As used herein, "biomarker value", "value", "biomarker level", and "level" are used interchangeably to refer to a measurement that is made using any analytical method for detecting the biomarker in a biological sample and that indicates the presence, absence, absolute amount or concentration, relative amount or concentration, titer, a level, an expression level, a ratio of measured levels, or the like, of, for, or corresponding to the biomarker in the biological sample. The exact nature of the "value" or "level" depends on the specific design and components of the particular analytical method employed to detect the biomarker.

When a biomarker indicates or is a sign of an abnormal process or a disease or other condition in an individual, that biomarker is generally described as being either over-expressed or under-expressed as compared to an expression level or value of the biomarker that indicates or is a sign of a normal process or an absence of a disease or other condition in an individual. "Up-regulation", "up-regulated", "over-expression", "over-expressed", and any variations thereof are used interchangeably to refer to a value or level of a biomarker in a biological sample that is greater than a value or level (or range of values or levels) of the biomarker that is typically detected in similar biological samples from healthy or normal individuals. The terms may also refer to a value or level of a biomarker in a biological sample that is greater than a value or level (or range of values or levels) of the biomarker that may be detected at a different stage of a particular disease.

"Down-regulation", "down-regulated", "under-expression", "under-expressed", and any variations thereof are used interchangeably to refer to a value or level of a biomarker in a biological sample that is less than a value or level (or range of values or levels) of the biomarker that is typically detected in similar biological samples from healthy or normal individuals. The terms may also refer to a value or level of a biomarker in a biological sample that is less than a value or level (or range of values or levels) of the biomarker that may be detected at a different stage of a particular disease.

Further, a biomarker that is either over-expressed or under-expressed can also be referred to as being "differentially expressed" or as having a "differential level" or "differential value" as compared to a "normal" expression level or value of the biomarker that indicates or is a sign of a normal process or an absence of a disease or other condition in an individual. Thus, "differential expression" of a biomarker can also be referred to as a variation from a "normal" expression level of the biomarker.

The term "differential gene expression" and "differential expression" are used interchangeably to refer to a gene (or its corresponding protein expression product) whose expression is activated to a higher or lower level in a subject suffering from a specific disease, relative to its expression in a normal or control subject. The terms also include genes (or the corresponding protein expression products) whose expression is activated to a higher or lower level at different stages of the same disease. It is also understood that a differentially expressed gene may be either activated or inhibited at the nucleic acid level or protein level, or may be subject to alternative splicing to result in a different polypeptide product. Such differences may be evidenced by a variety of changes including mRNA levels, surface expression, secretion or other partitioning of a polypeptide. Differential gene expression may include a comparison of

expression between two or more genes or their gene products; or a comparison of the ratios of the expression between two or more genes or their gene products; or even a comparison of two differently processed products of the same gene, which differ between normal subjects and subjects suffering from a disease; or between various stages of the same disease. Differential expression includes both quantitative, as well as qualitative, differences in the temporal or cellular expression pattern in a gene or its expression products among, for example, normal and diseased cells, or among cells which have undergone different disease events or disease stages.

As used herein, "individual" refers to a test subject or patient. The individual can be a mammal or a non-mammal. In various embodiments, the individual is a mammal. A mammalian individual can be a human or non-human. In various embodiments, the individual is a human. A healthy or normal individual is an individual in which the disease or condition of interest (including, for example, lung diseases, lung-associated diseases, or other lung conditions) is not detectable by conventional diagnostic methods.

"Diagnose", "diagnosing", "diagnosis", and variations thereof refer to the detection, determination, or recognition of a health status or condition of an individual on the basis of one or more signs, symptoms, data, or other information pertaining to that individual. The health status of an individual can be diagnosed as healthy/normal (i.e., a diagnosis of the absence of a disease or condition) or diagnosed as ill/abnormal (i.e., a diagnosis of the presence, or an assessment of the characteristics, of a disease or condition). The terms "diagnose", "diagnosing", "diagnosis", etc., encompass, with respect to a particular disease or condition, the initial detection of the disease; the characterization or classification of the disease; the detection of the progression, remission, or recurrence of the disease; and the detection of disease response after the administration of a treatment or therapy to the individual. The diagnosis of lung cancer includes distinguishing individuals, including smokers and nonsmokers, who have cancer from individuals who do not. It further includes distinguishing benign pulmonary nodules from cancerous pulmonary nodules.

"Prognose", "prognosing", "prognosis", and variations thereof refer to the prediction of a future course of a disease or condition in an individual who has the disease or condition (e.g., predicting patient survival), and such terms encompass the evaluation of disease response after the administration of a treatment or therapy to the individual.

"Evaluate", "evaluating", "evaluation", and variations thereof encompass both "diagnose" and "prognose" and also encompass determinations or predictions about the future course of a disease or condition in an individual who does not have the disease as well as determinations or predictions regarding the likelihood that a disease or condition will recur in an individual who apparently has been cured of the disease. The term "evaluate" also encompasses assessing an individual's response to a therapy, such as, for example, predicting whether an individual is likely to respond favorably to a therapeutic agent or is unlikely to respond to a therapeutic agent (or will experience toxic or other undesirable side effects, for example), selecting a therapeutic agent for administration to an individual, or monitoring or determining an individual's response to a therapy that has been administered to the individual. Thus, "evaluating" lung cancer can include, for example, any of the following: prognosing the future course of lung cancer in an individual; predicting the recurrence of lung cancer in an individual who apparently has been cured of lung cancer; or determining or predicting an individual's response to a lung cancer treatment or selecting a lung cancer treatment to administer to an individual based upon a determination of the biomarker values derived from the individual's biological sample.

Any of the following examples may be referred to as either "diagnosing" or "evaluating" lung cancer: initially detecting the presence or absence of lung cancer; determining a specific stage, type or sub-type, or other classification or characteristic of lung cancer; determining whether a pulmonary nodule is a benign lesion or a malignant lung tumor; or detecting/monitoring lung cancer progression (e.g., monitoring lung tumor growth or metastatic spread), remission, or recurrence.

As used herein, "additional biomedical information" refers to one or more evaluations of an individual, other than using any of the biomarkers described herein, that are associated with lung cancer risk. "Additional biomedical information" includes any of the following: physical descriptors of an individual, physical descriptors of a pulmonary nodule observed by CT imaging, the height and/or weight of an individual, the gender of an individual, the ethnicity of an individual, smoking history, occupational history, exposure to known carcinogens (e.g., exposure to any of asbestos, radon gas, chemicals, smoke from fires, and air pollution, which can include emissions from stationary or mobile sources such as industrial/factory or auto/marine/aircraft emissions), exposure to second-hand smoke, family history of lung cancer (or other cancer), the presence of pulmonary nodules, size of nodules, location of nodules, morphology of nodules (e.g., as observed through CT imaging, ground glass opacity (GGO), solid, non-solid), edge characteristics of the nodule (e.g., smooth, lobulated, sharp and smooth, spiculated, infiltrating), and the like. Smoking history is usually quantified in terms of "pack years", which refers to the number of years a person has smoked multiplied by the average number of packs smoked per day. For example, a person who has smoked, on average, one pack of cigarettes per day for 35 years is referred to as having 35 pack years of smoking history. Additional biomedical information can be obtained from an individual using routine techniques known in the art, such as from the individual themselves by use of a routine patient questionnaire or health history questionnaire, etc., or from a medical practitioner, etc. Alternately, additional biomedical information can be obtained from routine imaging techniques, including CT imaging (e.g., low-dose CT imaging) and X-ray. Testing of biomarker levels in combination with an evaluation of any additional biomedical information may, for example, improve sensitivity, specificity, and/or AUC for detecting lung cancer (or other lung cancer-related uses) as compared to biomarker testing alone or evaluating any particular item of additional biomedical information alone (e.g., CT imaging alone).

The term "area under the curve" or "AUC" refers to the area under the curve of a receiver operating characteristic (ROC) curve, both of which are well known in the art. AUC measures are useful for comparing the accuracy of a classifier across the complete data range. Classifiers with a greater AUC have a greater capacity to classify unknowns correctly between two groups of interest (e.g., lung cancer samples and normal or control samples). ROC curves are useful for plotting the performance of a particular feature (e.g., any of the biomarkers described herein and/or any item of additional biomedical information) in distinguishing between two populations (e.g., cases having lung cancer and controls without lung cancer). Typically, the feature data

across the entire population (e.g., the cases and controls) are sorted in ascending order based on the value of a single feature. Then, for each value for that feature, the true positive and false positive rates for the data are calculated. The true positive rate is determined by counting the number of cases above the value for that feature and then dividing by the total number of cases. The false positive rate is determined by counting the number of controls above the value for that feature and then dividing by the total number of controls. Although this definition refers to scenarios in which a feature is elevated in cases compared to controls, this definition also applies to scenarios in which a feature is lower in cases compared to the controls (in such a scenario, samples below the value for that feature would be counted). ROC curves can be generated for a single feature as well as for other single outputs, for example, a combination of two or more features can be mathematically combined (e.g., added, subtracted, multiplied, etc.) to provide a single sum value, and this single sum value can be plotted in a ROC curve. Additionally, any combination of multiple features, in which the combination derives a single output value, can be plotted in a ROC curve. These combinations of features may comprise a test. The ROC curve is the plot of the true positive rate (sensitivity) of a test against the false positive rate (1-specificity) of the test.

As used herein, "detecting" or "determining" with respect to a biomarker value includes the use of both the instrument required to observe and record a signal corresponding to a biomarker value and the material/s required to generate that signal. In various embodiments, the biomarker value is detected using any suitable method, including fluorescence, chemiluminescence, surface plasmon resonance, surface acoustic waves, mass spectrometry, infrared spectroscopy, Raman spectroscopy, atomic force microscopy, scanning tunneling microscopy, electrochemical detection methods, nuclear magnetic resonance, quantum dots, and the like.

"Solid support" refers herein to any substrate having a surface to which molecules may be attached, directly or indirectly, through either covalent or non-covalent bonds. A "solid support" can have a variety of physical formats, which can include, for example, a membrane; a chip (e.g., a protein chip); a slide (e.g., a glass slide or coverslip); a column; a hollow, solid, semi-solid, pore- or cavity-containing particle, such as, for example, a bead; a gel; a fiber, including a fiber optic material; a matrix; and a sample receptacle. Exemplary sample receptacles include sample wells, tubes, capillaries, vials, and any other vessel, groove or indentation capable of holding a sample. A sample receptacle can be contained on a multi-sample platform, such as a microtiter plate, slide, microfluidics device, and the like. A support can be composed of a natural or synthetic material, an organic or inorganic material. The composition of the solid support on which capture reagents are attached generally depends on the method of attachment (e.g., covalent attachment). Other exemplary receptacles include microdroplets and microfluidic controlled or bulk oil/aqueous emulsions within which assays and related manipulations can occur. Suitable solid supports include, for example, plastics, resins, polysaccharides, silica or silica-based materials, functionalized glass, modified silicon, carbon, metals, inorganic glasses, membranes, nylon, natural fibers (such as, for example, silk, wool and cotton), polymers, and the like. The material composing the solid support can include reactive groups such as, for example, carboxy, amino, or hydroxyl groups, which are used for attachment of the capture reagents. Polymeric solid supports can include, e.g., polystyrene, polyethylene glycol tetraphthalate, polyvinyl acetate, polyvinyl chloride, polyvinyl pyrrolidone, polyacrylonitrile, polymethyl methacrylate, polytetrafluoroethylene, butyl rubber, styrenebutadiene rubber, natural rubber, polyethylene, polypropylene, (poly)tetrafluoroethylene, (poly) vinylidenefluoride, polycarbonate, and polymethylpentene. Suitable solid support particles that can be used include, e.g., encoded particles, such as Luminex®-type encoded particles, magnetic particles, and glass particles.

Exemplary Uses of Biomarkers

In various exemplary embodiments, methods are provided for diagnosing lung cancer in an individual by detecting one or more biomarker values corresponding to one or more biomarkers that are present in the circulation of an individual, such as in serum or plasma, by any number of analytical methods, including any of the analytical methods described herein. These biomarkers are, for example, differentially expressed in individuals with lung cancer as compared to individuals without lung cancer. Detection of the differential expression of a biomarker in an individual can be used, for example, to permit the early diagnosis of lung cancer, to distinguish between a benign and malignant pulmonary nodule (such as, for example, a nodule observed on a computed tomography (CT) scan), to monitor lung cancer recurrence, or for other clinical indications.

Any of the biomarkers described herein may be used in a variety of clinical indications for lung cancer, including any of the following: detection of lung cancer (such as in a high-risk individual or population); characterizing lung cancer (e.g., determining lung cancer type, sub-type, or stage), such as by distinguishing between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) and/or between adenocarcinoma and squamous cell carcinoma (or otherwise facilitating histopathology); determining whether a lung nodule is a benign nodule or a malignant lung tumor; determining lung cancer prognosis; monitoring lung cancer progression or remission; monitoring for lung cancer recurrence; monitoring metastasis; treatment selection; monitoring response to a therapeutic agent or other treatment; stratification of individuals for computed tomography (CT) screening (e.g., identifying those individuals at greater risk of lung cancer and thereby most likely to benefit from spiral-CT screening, thus increasing the positive predictive value of CT); combining biomarker testing with additional biomedical information, such as smoking history, etc., or with nodule size, morphology, etc. (such as to provide an assay with increased diagnostic performance compared to CT testing or biomarker testing alone); facilitating the diagnosis of a pulmonary nodule as malignant or benign; facilitating clinical decision making once a pulmonary nodule is observed on CT (e.g., ordering repeat CT scans if the nodule is deemed to be low risk, such as if a biomarker-based test is negative, with or without categorization of nodule size, or considering biopsy if the nodule is deemed medium to high risk, such as if a biomarker-based test is positive, with or without categorization of nodule size); and facilitating decisions regarding clinical follow-up (e.g., whether to implement repeat CT scans, fine needle biopsy, or thoracotomy after observing a non-calcified nodule on CT). Biomarker testing may improve positive predictive value (PPV) over CT screening alone. In addition to their utilities in conjunction with CT screening, the biomarkers described herein can also be used in conjunction with any other imaging modalities used for lung cancer, such as chest X-ray. Furthermore, the described biomarkers may also be useful in permitting certain of these uses before indications of lung cancer are detected by imaging modalities or other clinical correlates, or before symptoms appear.

As an example of the manner in which any of the biomarkers described herein can be used to diagnose lung cancer, differential expression of one or more of the described biomarkers in an individual who is not known to have lung cancer may indicate that the individual has lung cancer, thereby enabling detection of lung cancer at an early stage of the disease when treatment is most effective, perhaps before the lung cancer is detected by other means or before symptoms appear. Over-expression of one or more of the biomarkers during the course of lung cancer may be indicative of lung cancer progression, e.g., a lung tumor is growing and/or metastasizing (and thus indicate a poor prognosis), whereas a decrease in the degree to which one or more of the biomarkers is differentially expressed (i.e., in subsequent biomarker tests, the expression level in the individual is moving toward or approaching a "normal" expression level) may be indicative of lung cancer remission, e.g., a lung tumor is shrinking (and thus indicate a good or better prognosis). Similarly, an increase in the degree to which one or more of the biomarkers is differentially expressed (i.e., in subsequent biomarker tests, the expression level in the individual is moving further away from a "normal" expression level) during the course of lung cancer treatment may indicate that the lung cancer is progressing and therefore indicate that the treatment is ineffective, whereas a decrease in differential expression of one or more of the biomarkers during the course of lung cancer treatment may be indicative of lung cancer remission and therefore indicate that the treatment is working successfully. Additionally, an increase or decrease in the differential expression of one or more of the biomarkers after an individual has apparently been cured of lung cancer may be indicative of lung cancer recurrence. In a situation such as this, for example, the individual can be re-started on therapy (or the therapeutic regimen modified such as to increase dosage amount and/or frequency, if the individual has maintained therapy) at an earlier stage than if the recurrence of lung cancer was not detected until later. Furthermore, a differential expression level of one or more of the biomarkers in an individual may be predictive of the individual's response to a particular therapeutic agent. In monitoring for lung cancer recurrence or progression, changes in the biomarker expression levels may indicate the need for repeat imaging (e.g., repeat CT scanning), such as to determine lung cancer activity or to determine the need for changes in treatment.

Detection of any of the biomarkers described herein may be particularly useful following, or in conjunction with, lung cancer treatment, such as to evaluate the success of the treatment or to monitor lung cancer remission, recurrence, and/or progression (including metastasis) following treatment. Lung cancer treatment may include, for example, administration of a therapeutic agent to the individual, performance of surgery (e.g., surgical resection of at least a portion of a lung tumor), administration of radiation therapy, or any other type of lung cancer treatment used in the art, and any combination of these treatments. For example, any of the biomarkers may be detected at least once after treatment or may be detected multiple times after treatment (such as at periodic intervals), or may be detected both before and after treatment. Differential expression levels of any of the biomarkers in an individual over time may be indicative of lung cancer progression, remission, or recurrence, examples of which include any of the following: an increase or decrease in the expression level of the biomarkers after treatment compared with the expression level of the biomarker before treatment; an increase or decrease in the expression level of the biomarker at a later time point after treatment compared with the expression level of the biomarker at an earlier time point after treatment; and a differential expression level of the biomarker at a single time point after treatment compared with normal levels of the biomarker.

As a specific example, the biomarker levels for any of the biomarkers described herein can be determined in pre-surgery and post-surgery (e.g., 2-4 weeks after surgery) serum samples. An increase in the biomarker expression level(s) in the post-surgery sample compared with the pre-surgery sample can indicate progression of lung cancer (e.g., unsuccessful surgery), whereas a decrease in the biomarker expression level(s) in the post-surgery sample compared with the pre-surgery sample can indicate regression of lung cancer (e.g., the surgery successfully removed the lung tumor). Similar analyses of the biomarker levels can be carried out before and after other forms of treatment, such as before and after radiation therapy or administration of a therapeutic agent or cancer vaccine.

In addition to testing biomarker levels as a stand-alone diagnostic test, biomarker levels can also be done in conjunction with determination of SNPs or other genetic lesions or variability that are indicative of increased risk of susceptibility of disease. (See, e.g., Amos et al., Nature Genetics 40, 616-622 (2009)).

In addition to testing biomarker levels as a stand-alone diagnostic test, biomarker levels can also be done in conjunction with CT screening. For example, the biomarkers may facilitate the medical and economic justification for implementing CT screening, such as for screening large asymptomatic populations at risk for lung cancer (e.g., smokers). For example, a "pre-CT" test of biomarker levels could be used to stratify high-risk individuals for CT screening, such as for identifying those who are at highest risk for lung cancer based on their biomarker levels and who should be prioritized for CT screening. If a CT test is implemented, biomarker levels (e.g., as determined by an aptamer assay of serum or plasma samples) of one or more biomarkers can be measured and the diagnostic score could be evaluated in conjunction with additional biomedical information (e.g., tumor parameters determined by CT testing) to enhance positive predictive value (PPV) over CT or biomarker testing alone. A "post-CT" aptamer panel for determining biomarker levels can be used to determine the likelihood that a pulmonary nodule observed by CT (or other imaging modality) is malignant or benign.

Detection of any of the biomarkers described herein may be useful for post-CT testing. For example, biomarker testing may eliminate or reduce a significant number of false positive tests over CT alone. Further, biomarker testing may facilitate treatment of patients. By way of example, if a lung nodule is less than 5 mm in size, results of biomarker testing may advance patients from "watch and wait" to biopsy at an earlier time; if a lung nodule is 5-9 mm, biomarker testing may eliminate the use of a biopsy or thoracotomy on false positive scans; and if a lung nodule is larger than 10 mm, biomarker testing may eliminate surgery for a sub-population of these patients with benign nodules. Eliminating the need for biopsy in some patients based on biomarker testing would be beneficial because there is significant morbidity associated with nodule biopsy and difficulty in obtaining nodule tissue depending on the location of nodule. Similarly, eliminating the need for surgery in some patients, such as those whose nodules are actually benign, would avoid unnecessary risks and costs associated with surgery.

In addition to testing biomarker levels in conjunction with CT screening (e.g., assessing biomarker levels in conjunc-

tion with size or other characteristics of a lung nodule observed on a CT scan), information regarding the biomarkers can also be evaluated in conjunction with other types of data, particularly data that indicates an individual's risk for lung cancer (e.g., patient clinical history, symptoms, family history of cancer, risk factors such as whether or not the individual is a smoker, and/or status of other biomarkers, etc.). These various data can be assessed by automated methods, such as a computer program/software, which can be embodied in a computer or other apparatus/device.

Any of the described biomarkers may also be used in imaging tests. For example, an imaging agent can be coupled to any of the described biomarkers, which can be used to aid in lung cancer diagnosis, to monitor disease progression/remission or metastasis, to monitor for disease recurrence, or to monitor response to therapy, among other uses.

Detection and Determination of Biomarkers and Biomarker Values

A biomarker value for the biomarkers described herein can be detected using any of a variety of known analytical methods. In one embodiment, a biomarker value is detected using a capture reagent. As used herein, a "capture agent' or "capture reagent" refers to a molecule that is capable of binding specifically to a biomarker. In various embodiments, the capture reagent can be exposed to the biomarker in solution or can be exposed to the biomarker while the capture reagent is immobilized on a solid support. In other embodiments, the capture reagent contains a feature that is reactive with a secondary feature on a solid support. In these embodiments, the capture reagent can be exposed to the biomarker in solution, and then the feature on the capture reagent can be used in conjunction with the secondary feature on the solid support to immobilize the biomarker on the solid support. The capture reagent is selected based on the type of analysis to be conducted. Capture reagents include but are not limited to aptamers, antibodies, adnectins, ankyrins, other antibody mimetics and other protein scaffolds, autoantibodies, chimeras, small molecules, an $F(ab')_2$ fragment, a single chain antibody fragment, an Fv fragment, a single chain Fv fragment, a nucleic acid, a lectin, a ligand-binding receptor, affybodies, nanobodies, imprinted polymers, avimers, peptidomimetics, a hormone receptor, a cytokine receptor, and synthetic receptors, and modifications and fragments of these.

In some embodiments, a biomarker value is detected using a biomarker/capture reagent complex.

In other embodiments, the biomarker value is derived from the biomarker/capture reagent complex and is detected indirectly, such as, for example, as a result of a reaction that is subsequent to the biomarker/capture reagent interaction, but is dependent on the formation of the biomarker/capture reagent complex.

In some embodiments, the biomarker value is detected directly from the biomarker in a biological sample.

In one embodiment, the biomarkers are detected using a multiplexed format that allows for the simultaneous detection of two or more biomarkers in a biological sample. In one embodiment of the multiplexed format, capture reagents are immobilized, directly or indirectly, covalently or non-covalently, in discrete locations on a solid support. In another embodiment, a multiplexed format uses discrete solid supports where each solid support has a unique capture reagent associated with that solid support, such as, for example quantum dots. In another embodiment, an individual device is used for the detection of each one of multiple biomarkers to be detected in a biological sample. Individual devices can be configured to permit each biomarker in the biological sample to be processed simultaneously. For example, a microtiter plate can be used such that each well in the plate is used to uniquely analyze one of multiple biomarkers to be detected in a biological sample.

In one or more of the foregoing embodiments, a fluorescent tag can be used to label a component of the biomarker/capture complex to enable the detection of the biomarker value. In various embodiments, the fluorescent label can be conjugated to a capture reagent specific to any of the biomarkers described herein using known techniques, and the fluorescent label can then be used to detect the corresponding biomarker value. Suitable fluorescent labels include rare earth chelates, fluorescein and its derivatives, rhodamine and its derivatives, dansyl, allophycocyanin, PBXL-3, Qdot 605, Lissamine, phycoerythrin, Texas Red, and other such compounds.

In one embodiment, the fluorescent label is a fluorescent dye molecule. In some embodiments, the fluorescent dye molecule includes at least one substituted indolium ring system in which the substituent on the 3-carbon of the indolium ring contains a chemically reactive group or a conjugated substance. In some embodiments, the dye molecule includes an AlexFluor molecule, such as, for example, AlexaFluor 488, AlexaFluor 532, AlexaFluor 647, AlexaFluor 680, or AlexaFluor 700. In other embodiments, the dye molecule includes a first type and a second type of dye molecule, such as, e.g., two different AlexaFluor molecules. In other embodiments, the dye molecule includes a first type and a second type of dye molecule, and the two dye molecules have different emission spectra.

Fluorescence can be measured with a variety of instrumentation compatible with a wide range of assay formats. For example, spectrofluorimeters have been designed to analyze microtiter plates, microscope slides, printed arrays, cuvettes, etc. See Principles of Fluorescence Spectroscopy, by J. R. Lakowicz, Springer Science+Business Media, Inc., 2004. See Bioluminescence & Chemiluminescence: Progress & Current Applications; Philip E. Stanley and Larry J. Kricka editors, World Scientific Publishing Company, January 2002.

In one or more of the foregoing embodiments, a chemiluminescence tag can optionally be used to label a component of the biomarker/capture complex to enable the detection of a biomarker value. Suitable chemiluminescent materials include any of oxalyl chloride, Rodamin 6G, $Ru(bipy)_3^{2+}$, TMAE (tetrakis(dimethylamino)ethylene), Pyrogallol (1,2,3-trihydroxibenzene), Lucigenin, peroxyoxalates, Aryl oxalates, Acridinium esters, dioxetanes, and others.

In yet other embodiments, the detection method includes an enzyme/substrate combination that generates a detectable signal that corresponds to the biomarker value. Generally, the enzyme catalyzes a chemical alteration of the chromogenic substrate which can be measured using various techniques, including spectrophotometry, fluorescence, and chemiluminescence. Suitable enzymes include, for example, luciferases, luciferin, malate dehydrogenase, urease, horseradish peroxidase (HRPO), alkaline phosphatase, beta-galactosidase, glucoamylase, lysozyme, glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, uricase, xanthine oxidase, lactoperoxidase, microperoxidase, and the like.

In yet other embodiments, the detection method can be a combination of fluorescence, chemiluminescence, radionuclide or enzyme/substrate combinations that generate a

measurable signal. Multimodal signaling could have unique and advantageous characteristics in biomarker assay formats.

More specifically, the biomarker values for the biomarkers described herein can be detected using known analytical methods including, singleplex aptamer assays, multiplexed aptamer assays, singleplex or multiplexed immunoassays, mRNA expression profiling, miRNA expression profiling, mass spectrometric analysis, histological/cytological methods, etc. as detailed below.

Determination of Biomarker Values Using Aptamer-Based Assays

Assays directed to the detection and quantification of physiologically significant molecules in biological samples and other samples are important tools in scientific research and in the health care field. One class of such assays involves the use of a microarray that includes one or more aptamers immobilized on a solid support. The aptamers are each capable of binding to a target molecule in a highly specific manner and with very high affinity. See, e.g., U.S. Pat. No. 5,475,096 entitled "Nucleic Acid Ligands"; see also, e.g., U.S. Pat. Nos. 6,242,246, 6,458,543, and U.S. Pat. No. 6,503,715, each of which is entitled "Nucleic Acid Ligand Diagnostic Biochip". Once the microarray is contacted with a sample, the aptamers bind to their respective target molecules present in the sample and thereby enable a determination of a biomarker value corresponding to a biomarker.

As used herein, an "aptamer" refers to a nucleic acid that has a specific binding affinity for a target molecule. It is recognized that affinity interactions are a matter of degree; however, in this context, the "specific binding affinity" of an aptamer for its target means that the aptamer binds to its target generally with a much higher degree of affinity than it binds to other components in a test sample. An "aptamer" is a set of copies of one type or species of nucleic acid molecule that has a particular nucleotide sequence. An aptamer can include any suitable number of nucleotides, including any number of chemically modified nucleotides. "Aptamers" refers to more than one such set of molecules. Different aptamers can have either the same or different numbers of nucleotides. Aptamers can be DNA or RNA or chemically modified nucleic acids and can be single stranded, double stranded, or contain double stranded regions, and can include higher ordered structures. An aptamer can also be a photoaptamer, where a photoreactive or chemically reactive functional group is included in the aptamer to allow it to be covalently linked to its corresponding target. Any of the aptamer methods disclosed herein can include the use of two or more aptamers that specifically bind the same target molecule. As further described below, an aptamer may include a tag. If an aptamer includes a tag, all copies of the aptamer need not have the same tag. Moreover, if different aptamers each include a tag, these different aptamers can have either the same tag or a different tag.

An aptamer can be identified using any known method, including the SELEX process. Once identified, an aptamer can be prepared or synthesized in accordance with any known method, including chemical synthetic methods and enzymatic synthetic methods.

The terms "SELEX" and "SELEX process" are used interchangeably herein to refer generally to a combination of (1) the selection of aptamers that interact with a target molecule in a desirable manner, for example binding with high affinity to a protein, with (2) the amplification of those selected nucleic acids. The SELEX process can be used to identify aptamers with high affinity to a specific target or biomarker.

SELEX generally includes preparing a candidate mixture of nucleic acids, binding of the candidate mixture to the desired target molecule to form an affinity complex, separating the affinity complexes from the unbound candidate nucleic acids, separating and isolating the nucleic acid from the affinity complex, purifying the nucleic acid, and identifying a specific aptamer sequence. The process may include multiple rounds to further refine the affinity of the selected aptamer. The process can include amplification steps at one or more points in the process. See, e.g., U.S. Pat. No. 5,475,096, entitled "Nucleic Acid Ligands". The SELEX process can be used to generate an aptamer that covalently binds its target as well as an aptamer that non-covalently binds its target. See, e.g., U.S. Pat. No. 5,705,337 entitled "Systematic Evolution of Nucleic Acid Ligands by Exponential Enrichment: Chemi-SELEX."

The SELEX process can be used to identify high-affinity aptamers containing modified nucleotides that confer improved characteristics on the aptamer, such as, for example, improved in vivo stability or improved delivery characteristics. Examples of such modifications include chemical substitutions at the ribose and/or phosphate and/or base positions. SELEX process-identified aptamers containing modified nucleotides are described in U.S. Pat. No. 5,660,985, entitled "High Affinity Nucleic Acid Ligands Containing Modified Nucleotides", which describes oligonucleotides containing nucleotide derivatives chemically modified at the 5'- and 2'-positions of pyrimidines. U.S. Pat. No. 5,580,737, see supra, describes highly specific aptamers containing one or more nucleotides modified with 2'-amino (2'-NH2), 2'-fluoro (2'-F), and/or 2'-O-methyl (2'-OMe). See also, U.S. Patent Application Publication 20090098549, entitled "SELEX and PHOTOSELEX", which describes nucleic acid libraries having expanded physical and chemical properties and their use in SELEX and photoSELEX.

SELEX can also be used to identify aptamers that have desirable off-rate characteristics. See U.S. Patent Application Publication 20090004667, entitled "Method for Generating Aptamers with Improved Off-Rates", which describes improved SELEX methods for generating aptamers that can bind to target molecules. Methods for producing aptamers and photoaptamers having slower rates of dissociation from their respective target molecules are described. The methods involve contacting the candidate mixture with the target molecule, allowing the formation of nucleic acid-target complexes to occur, and performing a slow off-rate enrichment process wherein nucleic acid-target complexes with fast dissociation rates will dissociate and not reform, while complexes with slow dissociation rates will remain intact. Additionally, the methods include the use of modified nucleotides in the production of candidate nucleic acid mixtures to generate aptamers with improved off-rate performance.

A variation of this assay employs aptamers that include photoreactive functional groups that enable the aptamers to covalently bind or "photocrosslink" their target molecules. See, e.g., U.S. Pat. No. 6,544,776 entitled "Nucleic Acid Ligand Diagnostic Biochip". These photoreactive aptamers are also referred to as photoaptamers. See, e.g., U.S. Pat. Nos. 5,763,177, 6,001,577, and 6,291,184, each of which is entitled "Systematic Evolution of Nucleic Acid Ligands by Exponential Enrichment: Photoselection of Nucleic Acid Ligands and Solution SELEX"; see also, e.g., U.S. Pat. No. 6,458,539, entitled "Photoselection of Nucleic Acid

Ligands". After the microarray is contacted with the sample and the photoaptamers have had an opportunity to bind to their target molecules, the photoaptamers are photoactivated, and the solid support is washed to remove any non-specifically bound molecules. Harsh wash conditions may be used, since target molecules that are bound to the photoaptamers are generally not removed, due to the covalent bonds created by the photoactivated functional group(s) on the photoaptamers. In this manner, the assay enables the detection of a biomarker value corresponding to a biomarker in the test sample.

In both of these assay formats, the aptamers are immobilized on the solid support prior to being contacted with the sample. Under certain circumstances, however, immobilization of the aptamers prior to contact with the sample may not provide an optimal assay. For example, pre-immobilization of the aptamers may result in inefficient mixing of the aptamers with the target molecules on the surface of the solid support, perhaps leading to lengthy reaction times and, therefore, extended incubation periods to permit efficient binding of the aptamers to their target molecules. Further, when photoaptamers are employed in the assay and depending upon the material utilized as a solid support, the solid support may tend to scatter or absorb the light used to effect the formation of covalent bonds between the photoaptamers and their target molecules. Moreover, depending upon the method employed, detection of target molecules bound to their aptamers can be subject to imprecision, since the surface of the solid support may also be exposed to and affected by any labeling agents that are used. Finally, immobilization of the aptamers on the solid support generally involves an aptamer-preparation step (i.e., the immobilization) prior to exposure of the aptamers to the sample, and this preparation step may affect the activity or functionality of the aptamers.

Aptamer assays that permit an aptamer to capture its target in solution and then employ separation steps that are designed to remove specific components of the aptamer-target mixture prior to detection have also been described (see U.S. Patent Application Publication 20090042206, entitled "Multiplexed Analyses of Test Samples"). The described aptamer assay methods enable the detection and quantification of a non-nucleic acid target (e.g., a protein target) in a test sample by detecting and quantifying a nucleic acid (i.e., an aptamer). The described methods create a nucleic acid surrogate (i.e, the aptamer) for detecting and quantifying a non-nucleic acid target, thus allowing the wide variety of nucleic acid technologies, including amplification, to be applied to a broader range of desired targets, including protein targets.

Aptamers can be constructed to facilitate the separation of the assay components from an aptamer biomarker complex (or photoaptamer biomarker covalent complex) and permit isolation of the aptamer for detection and/or quantification. In one embodiment, these constructs can include a cleavable or releasable element within the aptamer sequence. In other embodiments, additional functionality can be introduced into the aptamer, for example, a labeled or detectable component, a spacer component, or a specific binding tag or immobilization element. For example, the aptamer can include a tag connected to the aptamer via a cleavable moiety, a label, a spacer component separating the label, and the cleavable moiety. In one embodiment, a cleavable element is a photocleavable linker. The photocleavable linker can be attached to a biotin moiety and a spacer section, can include an NHS group for derivatization of amines, and can be used to introduce a biotin group to an aptamer, thereby allowing for the release of the aptamer later in an assay method.

Homogenous assays, done with all assay components in solution, do not require separation of sample and reagents prior to the detection of signal. These methods are rapid and easy to use. These methods generate signal based on a molecular capture or binding reagent that reacts with its specific target. For lung cancer, the molecular capture reagents would be an aptamer or an antibody or the like and the specific target would be a lung cancer biomarker of Table 1, Col. 2.

In one embodiment, a method for signal generation takes advantage of anisotropy signal change due to the interaction of a fluorophore-labeled capture reagent with its specific biomarker target. When the labeled capture reacts with its target, the increased molecular weight causes the rotational motion of the fluorophore attached to the complex to become much slower changing the anisotropy value. By monitoring the anisotropy change, binding events may be used to quantitatively measure the biomarkers in solutions. Other methods include fluorescence polarization assays, molecular beacon methods, time resolved fluorescence quenching, chemiluminescence, fluorescence resonance energy transfer, and the like.

An exemplary solution-based aptamer assay that can be used to detect a biomarker value corresponding to a biomarker in a biological sample includes the following: (a) preparing a mixture by contacting the biological sample with an aptamer that includes a first tag and has a specific affinity for the biomarker, wherein an aptamer affinity complex is formed when the biomarker is present in the sample; (b) exposing the mixture to a first solid support including a first capture element, and allowing the first tag to associate with the first capture element; (c) removing any components of the mixture not associated with the first solid support; (d) attaching a second tag to the biomarker component of the aptamer affinity complex; (e) releasing the aptamer affinity complex from the first solid support; (f) exposing the released aptamer affinity complex to a second solid support that includes a second capture element and allowing the second tag to associate with the second capture element; (g) removing any non-complexed aptamer from the mixture by partitioning the non-complexed aptamer from the aptamer affinity complex; (h) eluting the aptamer from the solid support; and (i) detecting the biomarker by detecting the aptamer component of the aptamer affinity complex.

Determination of Biomarker Values Using Immunoassays

Immunoassay methods are based on the reaction of an antibody to its corresponding target or analyte and can detect the analyte in a sample depending on the specific assay format. To improve specificity and sensitivity of an assay method based on immuno-reactivity, monoclonal antibodies are often used because of their specific epitope recognition. Polyclonal antibodies have also been successfully used in various immunoassays because of their increased affinity for the target as compared to monoclonal antibodies. Immunoassays have been designed for use with a wide range of biological sample matrices. Immunoassay formats have been designed to provide qualitative, semi-quantitative, and quantitative results.

Quantitative results are generated through the use of a standard curve created with known concentrations of the specific analyte to be detected. The response or signal from an unknown sample is plotted onto the standard curve, and a quantity or value corresponding to the target in the unknown sample is established.

Numerous immunoassay formats have been designed. ELISA or EIA can be quantitative for the detection of an analyte. This method relies on attachment of a label to either the analyte or the antibody and the label component includes, either directly or indirectly, an enzyme. ELISA tests may be formatted for direct, indirect, competitive, or sandwich detection of the analyte. Other methods rely on labels such as, for example, radioisotopes (I^{125}) or fluorescence. Additional techniques include, for example, agglutination, nephelometry, turbidimetry, Western blot, immunoprecipitation, immunocytochemistry, immunohistochemistry, flow cytometry, Luminex assay, and others (see ImmunoAssay: A Practical Guide, edited by Brian Law, published by Taylor & Francis, Ltd., 2005 edition).

Exemplary assay formats include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, fluorescent, chemiluminescence, and fluorescence resonance energy transfer (FRET) or time resolved-FRET (TR-FRET) immunoassays. Examples of procedures for detecting biomarkers include biomarker immunoprecipitation followed by quantitative methods that allow size and peptide level discrimination, such as gel electrophoresis, capillary electrophoresis, planar electrochromatography, and the like.

Methods of detecting and/or quantifying a detectable label or signal generating material depend on the nature of the label. The products of reactions catalyzed by appropriate enzymes (where the detectable label is an enzyme; see above) can be, without limitation, fluorescent, luminescent, or radioactive or they may absorb visible or ultraviolet light. Examples of detectors suitable for detecting such detectable labels include, without limitation, x-ray film, radioactivity counters, scintillation counters, spectrophotometers, colorimeters, fluorometers, luminometers, and densitometers.

Any of the methods for detection can be performed in any format that allows for any suitable preparation, processing, and analysis of the reactions. This can be, for example, in multi-well assay plates (e.g., 96 wells or 384 wells) or using any suitable array or microarray. Stock solutions for various agents can be made manually or robotically, and all subsequent pipetting, diluting, mixing, distribution, washing, incubating, sample readout, data collection and analysis can be done robotically using commercially available analysis software, robotics, and detection instrumentation capable of detecting a detectable label.

Determination of Biomarker Values Using Gene Expression Profiling

Measuring mRNA in a biological sample may be used as a surrogate for detection of the level of the corresponding protein in the biological sample. Thus, any of the biomarkers or biomarker panels described herein can also be detected by detecting the appropriate RNA.

mRNA expression levels are measured by reverse transcription quantitative polymerase chain reaction (RT-PCR followed with qPCR). RT-PCR is used to create a cDNA from the mRNA. The cDNA may be used in a qPCR assay to produce fluorescence as the DNA amplification process progresses. By comparison to a standard curve, qPCR can produce an absolute measurement such as number of copies of mRNA per cell. Northern blots, microarrays, Invader assays, and RT-PCR combined with capillary electrophoresis have all been used to measure expression levels of mRNA in a sample. See Gene Expression Profiling: Methods and Protocols, Richard A. Shimkets, editor, Humana Press, 2004.

miRNA molecules are small RNAs that are non-coding but may regulate gene expression. Any of the methods suited to the measurement of mRNA expression levels can also be used for the corresponding miRNA. Recently many laboratories have investigated the use of miRNAs as biomarkers for disease. Many diseases involve wide-spread transcriptional regulation, and it is not surprising that miRNAs might find a role as biomarkers. The connection between miRNA concentrations and disease is often even less clear than the connections between protein levels and disease, yet the value of miRNA biomarkers might be substantial. Of course, as with any RNA expressed differentially during disease, the problems facing the development of an in vitro diagnostic product will include the requirement that the miRNAs survive in the diseased cell and are easily extracted for analysis, or that the miRNAs are released into blood or other matrices where they must survive long enough to be measured. Protein biomarkers have similar requirements, although many potential protein biomarkers are secreted intentionally at the site of pathology and function, during disease, in a paracrine fashion. Many potential protein biomarkers are designed to function outside the cells within which those proteins are synthesized.

Detection of Biomarkers Using In Vivo Molecular Imaging Technologies

Any of the described biomarkers (see Table 1, Col. 2) may also be used in molecular imaging tests. For example, an imaging agent can be coupled to any of the described biomarkers, which can be used to aid in lung cancer diagnosis, to monitor disease progression/remission or metastasis, to monitor for disease recurrence, or to monitor response to therapy, among other uses.

In vivo imaging technologies provide non-invasive methods for determining the state of a particular disease in the body of an individual. For example, entire portions of the body, or even the entire body, may be viewed as a three dimensional image, thereby providing valuable information concerning morphology and structures in the body. Such technologies may be combined with the detection of the biomarkers described herein to provide information concerning the cancer status, in particular the lung cancer status, of an individual.

The use of in vivo molecular imaging technologies is expanding due to various advances in technology. These advances include the development of new contrast agents or labels, such as radiolabels and/or fluorescent labels, which can provide strong signals within the body; and the development of powerful new imaging technology, which can detect and analyze these signals from outside the body, with sufficient sensitivity and accuracy to provide useful information. The contrast agent can be visualized in an appropriate imaging system, thereby providing an image of the portion or portions of the body in which the contrast agent is located. The contrast agent may be bound to or associated with a capture reagent, such as an aptamer or an antibody, for example, and/or with a peptide or protein, or an oligonucleotide (for example, for the detection of gene expression), or a complex containing any of these with one or more macromolecules and/or other particulate forms.

The contrast agent may also feature a radioactive atom that is useful in imaging. Suitable radioactive atoms include technetium-99m or iodine-123 for scintigraphic studies. Other readily detectable moieties include, for example, spin labels for magnetic resonance imaging (MRI) such as, for example, iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron. Such labels are well known in the art and could easily be selected by one of ordinary skill in the art.

Standard imaging techniques include but are not limited to magnetic resonance imaging, computed tomography scanning, positron emission tomography (PET), single photon emission computed tomography (SPECT), and the like. For diagnostic in vivo imaging, the type of detection instrument available is a major factor in selecting a given contrast agent, such as a given radionuclide and the particular biomarker that it is used to target (protein, mRNA, and the like). The radionuclide chosen typically has a type of decay that is detectable by a given type of instrument. Also, when selecting a radionuclide for in vivo diagnosis, its half-life should be long enough to enable detection at the time of maximum uptake by the target tissue but short enough that deleterious radiation of the host is minimized.

Exemplary imaging techniques include but are not limited to PET and SPECT, which are imaging techniques in which a radionuclide is synthetically or locally administered to an individual. The subsequent uptake of the radiotracer is measured over time and used to obtain information about the targeted tissue and the biomarker. Because of the high-energy (gamma-ray) emissions of the specific isotopes employed and the sensitivity and sophistication of the instruments used to detect them, the two-dimensional distribution of radioactivity may be inferred from outside of the body.

Commonly used positron-emitting nuclides in PET include, for example, carbon-11, nitrogen-13, oxygen-15, and fluorine-18. Isotopes that decay by electron capture and/or gamma-emission are used in SPECT and include, for example iodine-123 and technetium-99m. An exemplary method for labeling amino acids with technetium-99m is the reduction of pertechnetate ion in the presence of a chelating precursor to form the labile technetium-99m-precursor complex, which, in turn, reacts with the metal binding group of a bifunctionally modified chemotactic peptide to form a technetium-99m-chemotactic peptide conjugate.

Antibodies are frequently used for such in vivo imaging diagnostic methods. The preparation and use of antibodies for in vivo diagnosis is well known in the art. Labeled antibodies which specifically bind any of the biomarkers in Table 1, Col. 2 can be injected into an individual suspected of having a certain type of cancer (e.g., lung cancer), detectable according to the particular biomarker used, for the purpose of diagnosing or evaluating the disease status of the individual. The label used will be selected in accordance with the imaging modality to be used, as previously described. Localization of the label permits determination of the spread of the cancer. The amount of label within an organ or tissue also allows determination of the presence or absence of cancer in that organ or tissue.

Similarly, aptamers may be used for such in vivo imaging diagnostic methods. For example, an aptamer that was used to identify a particular biomarker described in Table 1, Col. 2 (and therefore binds specifically to that particular biomarker) may be appropriately labeled and injected into an individual suspected of having lung cancer, detectable according to the particular biomarker, for the purpose of diagnosing or evaluating the lung cancer status of the individual. The label used will be selected in accordance with the imaging modality to be used, as previously described. Localization of the label permits determination of the spread of the cancer. The amount of label within an organ or tissue also allows determination of the presence or absence of cancer in that organ or tissue. Aptamer-directed imaging agents could have unique and advantageous characteristics relating to tissue penetration, tissue distribution, kinetics, elimination, potency, and selectivity as compared to other imaging agents.

Such techniques may also optionally be performed with labeled oligonucleotides, for example, for detection of gene expression through imaging with antisense oligonucleotides. These methods are used for in situ hybridization, for example, with fluorescent molecules or radionuclides as the label. Other methods for detection of gene expression include, for example, detection of the activity of a reporter gene.

Another general type of imaging technology is optical imaging, in which fluorescent signals within the subject are detected by an optical device that is external to the subject. These signals may be due to actual fluorescence and/or to bioluminescence. Improvements in the sensitivity of optical detection devices have increased the usefulness of optical imaging for in vivo diagnostic assays.

The use of in vivo molecular biomarker imaging is increasing, including for clinical trials, for example, to more rapidly measure clinical efficacy in trials for new cancer therapies and/or to avoid prolonged treatment with a placebo for those diseases, such as multiple sclerosis, in which such prolonged treatment may be considered to be ethically questionable.

For a review of other techniques, see N. Blow, Nature Methods, 6, 465-469, 2009.

Determination of Biomarker Values Using Histology/Cytology Methods

For evaluation of lung cancer, a variety of tissue samples may be used in histological or cytological methods. Sample selection depends on the primary tumor location and sites of metastases. For example, endo- and trans-bronchial biopsies, fine needle aspirates, cutting needles, and core biopsies can be used for histology. Bronchial washing and brushing, pleural aspiration, and sputum, can be used for cyotology. While cytological analysis is still used in the diagnosis of lung cancer, histological methods are known to provide better sensitivity for the detection of cancer. Any of the biomarkers identified herein that were shown to be up-regulated (see Table 37) in the individuals with lung cancer can be used to stain a histological specimen as an indication of disease.

In one embodiment, one or more capture reagent/s specific to the corresponding biomarker/s are used in a cytological evaluation of a lung cell sample and may include one or more of the following: collecting a cell sample, fixing the cell sample, dehydrating, clearing, immobilizing the cell sample on a microscope slide, permeabilizing the cell sample, treating for analyte retrieval, staining, destaining, washing, blocking, and reacting with one or more capture reagent/s in a buffered solution. In another embodiment, the cell sample is produced from a cell block.

In another embodiment, one or more capture reagent/s specific to the corresponding biomarkers are used in a histological evaluation of a lung tissue sample and may include one or more of the following: collecting a tissue specimen, fixing the tissue sample, dehydrating, clearing, immobilizing the tissue sample on a microscope slide, permeabilizing the tissue sample, treating for analyte retrieval, staining, destaining, washing, blocking, rehydrating, and reacting with capture reagent/s in a buffered solution. In another embodiment, fixing and dehydrating are replaced with freezing.

In another embodiment, the one or more aptamer/s specific to the corresponding biomarker/s are reacted with the histological or cytological sample and can serve as the nucleic acid target in a nucleic acid amplification method. Suitable nucleic acid amplification methods include, for example, PCR, q-beta replicase, rolling circle amplification,

strand displacement, helicase dependent amplification, loop mediated isothermal amplification, ligase chain reaction, and restriction and circularization aided rolling circle amplification.

In one embodiment, the one or more capture reagent/s specific to the corresponding biomarkers for use in the histological or cytological evaluation are mixed in a buffered solution that can include any of the following: blocking materials, competitors, detergents, stabilizers, carrier nucleic acid, polyanionic materials, etc.

A "cytology protocol" generally includes sample collection, sample fixation, sample immobilization, and staining. "Cell preparation" can include several processing steps after sample collection, including the use of one or more slow off-rate aptamers for the staining of the prepared cells.

Sample collection can include directly placing the sample in an untreated transport container, placing the sample in a transport container containing some type of media, or placing the sample directly onto a slide (immobilization) without any treatment or fixation.

Sample immobilization can be improved by applying a portion of the collected specimen to a glass slide that is treated with polylysine, gelatin, or a silane. Slides can be prepared by smearing a thin and even layer of cells across the slide. Care is generally taken to minimize mechanical distortion and drying artifacts. Liquid specimens can be processed in a cell block method. Or, alternatively, liquid specimens can be mixed 1:1 with the fixative solution for about 10 minutes at room temperature.

Cell blocks can be prepared from residual effusions, sputum, urine sediments, gastrointestinal fluids, cell scraping, or fine needle aspirates. Cells are concentrated or packed by centrifugation or membrane filtration. A number of methods for cell block preparation have been developed. Representative procedures include the fixed sediment, bacterial agar, or membrane filtration methods. In the fixed sediment method, the cell sediment is mixed with a fixative like Bouins, picric acid, or buffered formalin and then the mixture is centrifuged to pellet the fixed cells. The supernatant is removed, drying the cell pellet as completely as possible. The pellet is collected and wrapped in lens paper and then placed in a tissue cassette. The tissue cassette is placed in a jar with additional fixative and processed as a tissue sample. Agar method is very similar but the pellet is removed and dried on paper towel and then cut in half. The cut side is placed in a drop of melted agar on a glass slide and then the pellet is covered with agar making sure that no bubbles form in the agar. The agar is allowed to harden and then any excess agar is trimmed away. This is placed in a tissue cassette and the tissue process completed. Alternatively, the pellet may be directly suspended in 2% liquid agar at 65° C. and the sample centrifuged. The agar cell pellet is allowed to solidify for an hour at 4° C. The solid agar may be removed from the centrifuge tube and sliced in half. The agar is wrapped in filter paper and then the tissue cassette. Processing from this point forward is as described above. Centrifugation can be replaced in any these procedures with membrane filtration. Any of these processes may be used to generate a "cell block sample".

Cell blocks can be prepared using specialized resin including Lowicryl resins, LR White, LR Gold, Unicryl, and MonoStep. These resins have low viscosity and can be polymerized at low temperatures and with ultra violet (UV) light. The embedding process relies on progressively cooling the sample during dehydration, transferring the sample to the resin, and polymerizing a block at the final low temperature at the appropriate UV wavelength.

Cell block sections can be stained with hematoxylin-eosin for cytomorphological examination while additional sections are used for examination for specific markers.

Whether the process is cytologoical or histological, the sample may be fixed prior to additional processing to prevent sample degradation. This process is called "fixation" and describes a wide range of materials and procedures that may be used interchangeably. The sample fixation protocol and reagents are best selected empirically based on the targets to be detected and the specific cell/tissue type to be analyzed. Sample fixation relies on reagents such as ethanol, polyethylene glycol, methanol, formalin, or isopropanol. The samples should be fixed as soon after collection and affixation to the slide as possible. However, the fixative selected can introduce structural changes into various molecular targets making their subsequent detection more difficult. The fixation and immobilization processes and their sequence can modify the appearance of the cell and these changes must be anticipated and recognized by the cytotechnologist. Fixatives can cause shrinkage of certain cell types and cause the cytoplasm to appear granular or reticular. Many fixatives function by crosslinking cellular components. This can damage or modify specific epitopes, generate new epitopes, cause molecular associations, and reduce membrane permeability. Formalin fixation is one of the most common cytological/histological approaches. Formalin forms methyl bridges between neighboring proteins or within proteins. Precipitation or coagulation is also used for fixation and ethanol is frequently used in this type of fixation. A combination of crosslinking and precipitation can also be used for fixation. A strong fixation process is best at preserving morphological information while a weaker fixation process is best for the preservation of molecular targets.

A representative fixative is 50% absolute ethanol, 2 mM polyethylene glycol (PEG), 1.85% formaldehyde. Variations on this formulation include ethanol (50% to 95%), methanol (20%-50%), and formalin (formaldehyde) only. Another common fixative is 2% PEG 1500, 50% ethanol, and 3% methanol. Slides are place in the fixative for about 10 to 15 minutes at room temperature and then removed and allowed to dry. Once slides are fixed they can be rinsed with a buffered solution like PBS.

A wide range of dyes can be used to differentially highlight and contrast or "stain" cellular, sub-cellular, and tissue features or morphological structures. Hematoylin is used to stain nuclei a blue or black color. Orange G-6 and Eosin Azure both stain the cell's cytoplasm. Orange G stains keratin and glycogen containing cells yellow. Eosin Y is used to stain nucleoli, cilia, red blood cells, and superficial epithelial squamous cells. Romanowsky stains are used for air dried slides and are useful in enhancing pleomorphism and distinguishing extracellular from intracytoplasmic material.

The staining process can include a treatment to increase the permeability of the cells to the stain. Treatment of the cells with a detergent can be used to increase permeability. To increase cell and tissue permeability, fixed samples can be further treated with solvents, saponins, or non-ionic detergents. Enzymatic digestion can also improve the accessibility of specific targets in a tissue sample.

After staining, the sample is dehydrated using a succession of alcohol rinses with increasing alcohol concentration. The final wash is done with xylene or a xylene substitute, such as a citrus terpene, that has a refractive index close to that of the coverslip to be applied to the slide. This final step is referred to as clearing. Once the sample is dehydrated and cleared, a mounting medium is applied. The mounting

medium is selected to have a refractive index close to the glass and is capable of bonding the coverslip to the slide. It will also inhibit the additional drying, shrinking, or fading of the cell sample.

Regardless of the stains or processing used, the final evaluation of the lung cytological specimen is made by some type of microscopy to permit a visual inspection of the morphology and a determination of the marker's presence or absence. Exemplary microscopic methods include bright-field, phase contrast, fluorescence, and differential interference contrast.

If secondary tests are required on the sample after examination, the coverslip may be removed and the slide destained. Destaining involves using the original solvent systems used in staining the slide originally without the added dye and in a reverse order to the original staining procedure. Destaining may also be completed by soaking the slide in an acid alcohol until the cells are colorless. Once colorless the slides are rinsed well in a water bath and the second staining procedure applied.

In addition, specific molecular differentiation may be possible in conjunction with the cellular morphological analysis through the use of specific molecular reagents such as antibodies or nucleic acid probes or aptamers. This improves the accuracy of diagnostic cytology. Micro-dissection can be used to isolate a subset of cells for additional evaluation, in particular, for genetic evaluation of abnormal chromosomes, gene expression, or mutations.

Preparation of a tissue sample for histological evaluation involves fixation, dehydration, infiltration, embedding, and sectioning. The fixation reagents used in histology are very similar or identical to those used in cytology and have the same issues of preserving morphological features at the expense of molecular ones such as individual proteins. Time can be saved if the tissue sample is not fixed and dehydrated but instead is frozen and then sectioned while frozen. This is a more gentle processing procedure and can preserve more individual markers. However, freezing is not acceptable for long term storage of a tissue sample as subcellular information is lost due to the introduction of ice crystals. Ice in the frozen tissue sample also prevents the sectioning process from producing a very thin slice and thus some microscopic resolution and imaging of subcellular structures can be lost. In addition to formalin fixation, osmium tetroxide is used to fix and stain phospholipids (membranes).

Dehydration of tissues is accomplished with successive washes of increasing alcohol concentration. Clearing employs a material that is miscible with alcohol and the embedding material and involves a stepwise process starting at 50:50 alcohol:clearing reagent and then 100% clearing agent (xylene or xylene substitute). Infiltration involves incubating the tissue with a liquid form of the embedding agent (warm wax, nitrocellulose solution) first at 50:50 embedding agent: clearing agent and the 100% embedding agent. Embedding is completed by placing the tissue in a mold or cassette and filling with melted embedding agent such as wax, agar, or gelatin. The embedding agent is allowed to harden. The hardened tissue sample may then be sliced into thin section for staining and subsequent examination.

Prior to staining, the tissue section is dewaxed and rehydrated. Xylene is used to dewax the section, one or more changes of xylene may be used, and the tissue is rehydrated by successive washes in alcohol of decreasing concentration. Prior to dewax, the tissue section may be heat immobilized to a glass slide at about 80° C. for about 20 minutes.

Laser capture micro-dissection allows the isolation of a subset of cells for further analysis from a tissue section.

As in cytology, to enhance the visualization of the microscopic features, the tissue section or slice can be stained with a variety of stains. A large menu of commercially available stains can be used to enhance or identify specific features.

To further increase the interaction of molecular reagents with cytological/histological samples, a number of techniques for "analyte retrieval" have been developed. The first such technique uses high temperature heating of a fixed sample. This method is also referred to as heat-induced epitope retrieval or HIER. A variety of heating techniques have been used, including steam heating, microwaving, autoclaving, water baths, and pressure cooking or a combination of these methods of heating. Analyte retrieval solutions include, for example, water, citrate, and normal saline buffers. The key to analyte retrieval is the time at high temperature but lower temperatures for longer times have also been successfully used. Another key to analyte retrieval is the pH of the heating solution. Low pH has been found to provide the best immunostaining but also gives rise to backgrounds that frequently require the use of a second tissue section as a negative control. The most consistent benefit (increased immunostaining without increase in background) is generally obtained with a high pH solution regardless of the buffer composition. The analyte retrieval process for a specific target is empirically optimized for the target using heat, time, pH, and buffer composition as variables for process optimization. Using the microwave analyte retrieval method allows for sequential staining of different targets with antibody reagents. But the time required to achieve antibody and enzyme complexes between staining steps has also been shown to degrade cell membrane analytes. Microwave heating methods have improved in situ hybridization methods as well.

To initiate the analyte retrieval process, the section is first dewaxed and hydrated. The slide is then placed in 10 mM sodium citrate buffer pH 6.0 in a dish or jar. A representative procedure uses an 1100W microwave and microwaves the slide at 100% power for 2 minutes followed by microwaving the slides using 20% power for 18 minutes after checking to be sure the slide remains covered in liquid. The slide is then allowed to cool in the uncovered container and then rinsed with distilled water. HIER may be used in combination with an enzymatic digestion to improve the reactivity of the target to immunochemical reagents.

One such enzymatic digestion protocol uses proteinase K. A 20 μg/ml concentration of proteinase K is prepared in 50 mM Tris Base, 1 mM EDTA, 0.5% Triton X-100, pH 8.0 buffer. The process first involves dewaxing sections in 2 changes of xylene, 5 minutes each. Then the sample is hydrated in 2 changes of 100% ethanol for 3 minutes each, 95% and 80% ethanol for 1 minute each, and then rinsed in distilled water. Sections are covered with Proteinase K working solution and incubated 10-20 minutes at 37° C. in humidified chamber (optimal incubation time may vary depending on tissue type and degree of fixation). The sections are cooled at room temperature for 10 minutes and then rinsed in PBS Tween 20 for 2×2 min. If desired, sections can be blocked to eliminate potential interference from endogenous compounds and enzymes. The section is then incubated with primary antibody at appropriate dilution in primary antibody dilution buffer for 1 hour at room temperature or overnight at 4° C. The section is then rinsed with PBS Tween 20 for 2×2 min. Additional blocking can be performed, if required for the specific application, followed

by additional rinsing with PBS Tween 20 for 3×2 min. and then finally the immunostaining protocol completed.

A simple treatment with 1% SDS at room temperature has also been demonstrated to improve immunohistochemical staining. Analyte retrieval methods have been applied to slide mounted sections as well as free floating sections. Another treatment option is to place the slide in a jar containing citric acid and 0.1 Nonident P40 at pH 6.0 and heating to 95° C. The slide is then washed with a buffer solution like PBS.

For immunological staining of tissues it may be useful to block non-specific association of the antibody with tissue proteins by soaking the section in a protein solution like serum or non-fat dry milk.

Blocking reactions may include the need to reduce the level of endogenous biotin; eliminate endogenous charge effects; inactivate endogenous nucleases; and/or inactivate endogenous enzymes like peroxidase and alkaline phosphatase. Endogenous nucleases may be inactivated by degradation with proteinase K, by heat treatment, use of a chelating agent such as EDTA or EGTA, the introduction of carrier DNA or RNA, treatment with a chaotrope such as urea, thiourea, guanidine hydrochloride, guanidine thiocyanate, lithium perchlorate, etc, or diethyl pyrocarbonate. Alkaline phosphatase may be inactivated by treated with 0.1N HCl for 5 minutes at room temperature or treatment with 1 mM levamisole. Peroxidase activity may be eliminated by treatment with 0.03% hydrogen peroxide. Endogenous biotin may be blocked by soaking the slide or section in an avidin (streptavidin, neutravidin may be substituted) solution for at least 15 minutes at room temperature. The slide or section is then washed for at least 10 minutes in buffer. This may be repeated at least three times. Then the slide or section is soaked in a biotin solution for 10 minutes. This may be repeated at least three times with a fresh biotin solution each time. The buffer wash procedure is repeated. Blocking protocols should be minimized to prevent damaging either the cell or tissue structure or the target or targets of interest but one or more of these protocols could be combined to "block" a slide or section prior to reaction with one or more slow off-rate aptamers. See Basic Medical Histology: the Biology of Cells, Tissues and Organs, authored by Richard G. Kessel, Oxford University Press, 1998.

Determination of Biomarker Values Using Mass Spectrometry Methods

A variety of configurations of mass spectrometers can be used to detect biomarker values. Several types of mass spectrometers are available or can be produced with various configurations. In general, a mass spectrometer has the following major components: a sample inlet, an ion source, a mass analyzer, a detector, a vacuum system, and instrument-control system, and a data system. Difference in the sample inlet, ion source, and mass analyzer generally define the type of instrument and its capabilities. For example, an inlet can be a capillary-column liquid chromatography source or can be a direct probe or stage such as used in matrix-assisted laser desorption. Common ion sources are, for example, electrospray, including nanospray and microspray or matrix-assisted laser desorption. Common mass analyzers include a quadrupole mass filter, ion trap mass analyzer and time-of-flight mass analyzer. Additional mass spectrometry methods are well known in the art (see Burlingame et al. Anal. Chem. 70:647 R-716R (1998); Kinter and Sherman, New York (2000)).

Protein biomarkers and biomarker values can be detected and measured by any of the following: electrospray ionization mass spectrometry (ESI-MS), ESI-MS/MS, ESI-MS/(MS)n, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS), surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS), desorption/ionization on silicon (DIOS), secondary ion mass spectrometry (SIMS), quadrupole time-of-flight (Q-TOF), tandem time-of-flight (TOF/TOF) technology, called ultraflex III TOF/TOF, atmospheric pressure chemical ionization mass spectrometry (APCI-MS), APCI-MS/MS, APCI-$(MS)^N$, atmospheric pressure photoionization mass spectrometry (APPI-MS), APPI-MS/MS, and APPI-$(MS)^N$, quadrupole mass spectrometry, Fourier transform mass spectrometry (FTMS), quantitative mass spectrometry, and ion trap mass spectrometry.

Sample preparation strategies are used to label and enrich samples before mass spectroscopic characterization of protein biomarkers and determination biomarker values. Labeling methods include but are not limited to isobaric tag for relative and absolute quantitation (iTRAQ) and stable isotope labeling with amino acids in cell culture (SILAC). Capture reagents used to selectively enrich samples for candidate biomarker proteins prior to mass spectroscopic analysis include but are not limited to aptamers, antibodies, nucleic acid probes, chimeras, small molecules, an $F(ab')_2$ fragment, a single chain antibody fragment, an Fv fragment, a single chain Fv fragment, a nucleic acid, a lectin, a ligand-binding receptor, affybodies, nanobodies, ankyrins, domain antibodies, alternative antibody scaffolds (e.g. diabodies etc) imprinted polymers, avimers, peptidomimetics, peptoids, peptide nucleic acids, threose nucleic acid, a hormone receptor, a cytokine receptor, and synthetic receptors, and modifications and fragments of these.

The foregoing assays enable the detection of biomarker values that are useful in methods for diagnosing lung cancer, where the methods comprise detecting, in a biological sample from an individual, at least N biomarker values that each correspond to a biomarker selected from the group consisting of the biomarkers provided in Table 1, Col. 2, wherein a classification, as described in detail below, using the biomarker values indicates whether the individual has lung cancer. While certain of the described lung cancer biomarkers are useful alone for detecting and diagnosing lung cancer, methods are also described herein for the grouping of multiple subsets of the lung cancer biomarkers that are each useful as a panel of three or more biomarkers. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least three biomarkers. In other embodiments, N is selected to be any number from 2-61 biomarkers. It will be appreciated that N can be selected to be any number from any of the above described ranges, as well as similar, but higher order, ranges. In accordance with any of the methods described herein, biomarker values can be detected and classified individually or they can be detected and classified collectively, as for example in a multiplex assay format.

In another aspect, methods are provided for detecting an absence of lung cancer, the methods comprising detecting, in a biological sample from an individual, at least N biomarker values that each correspond to a biomarker selected from the group consisting of the biomarkers provided in Table 1, Col. 2, wherein a classification, as described in detail below, of the biomarker values indicates an absence of lung cancer in the individual. While certain of the described lung cancer biomarkers are useful alone for detecting and diagnosing the absence of lung cancer, methods are also described herein for the grouping of multiple subsets of the lung cancer

biomarkers that are each useful as a panel of three or more biomarkers. Thus, various embodiments of the instant application provide combinations comprising N biomarkers, wherein N is at least three biomarkers. In other embodiments, N is selected to be any number from 2-61 biomarkers. It will be appreciated that N can be selected to be any number from any of the above described ranges, as well as similar, but higher order, ranges. In accordance with any of the methods described herein, biomarker values can be detected and classified individually or they can be detected and classified collectively, as for example in a multiplex assay format.

Classification of Biomarkers and Calculation of Disease Scores

A biomarker "signature" for a given diagnostic test contains a set of markers, each marker having different levels in the populations of interest. Different levels, in this context, may refer to different means of the marker levels for the individuals in two or more groups, or different variances in the two or more groups, or a combination of both. For the simplest form of a diagnostic test, these markers can be used to assign an unknown sample from an individual into one of two groups, either diseased or not diseased. The assignment of a sample into one of two or more groups is known as classification, and the procedure used to accomplish this assignment is known as a classifier or a classification method. Classification methods may also be referred to as scoring methods. There are many classification methods that can be used to construct a diagnostic classifier from a set of biomarker values. In general, classification methods are most easily performed using supervised learning techniques where a data set is collected using samples obtained from individuals within two (or more, for multiple classification states) distinct groups one wishes to distinguish. Since the class (group or population) to which each sample belongs is known in advance for each sample, the classification method can be trained to give the desired classification response. It is also possible to use unsupervised learning techniques to produce a diagnostic classifier.

Common approaches for developing diagnostic classifiers include decision trees; bagging+boosting+forests; rule inference based learning; Parzen Windows; linear models; logistic; neural network methods; unsupervised clustering; K-means; hierarchical ascending/descending; semi-supervised learning; prototype methods; nearest neighbor; kernel density estimation; support vector machines; hidden Markov models; Boltzmann Learning; and classifiers may be combined either simply or in ways which minimize particular objective functions. For a review, see, e.g., Pattern Classification, R. O. Duda, et al., editors, John Wiley & Sons, 2nd edition, 2001; see also, The Elements of Statistical Learning—Data Mining, Inference, and Prediction, T. Hastie, et al., editors, Springer Science+Business Media, LLC, 2nd edition, 2009; each of which is incorporated by reference in its entirety.

To produce a classifier using supervised learning techniques, a set of samples called training data are obtained. In the context of diagnostic tests, training data includes samples from the distinct groups (classes) to which unknown samples will later be assigned. For example, samples collected from individuals in a control population and individuals in a particular disease population can constitute training data to develop a classifier that can classify unknown samples (or, more particularly, the individuals from whom the samples were obtained) as either having the disease or being free from the disease. The development of the classifier from the training data is known as training the classifier. Specific details on classifier training depend on the nature of the supervised learning technique. For purposes of illustration, an example of training a naïve Bayesian classifier will be described below (see, e.g., Pattern Classification, R. O. Duda, et al., editors, John Wiley & Sons, 2nd edition, 2001; see also, The Elements of Statistical Learning—Data Mining, Inference, and Prediction, T. Hastie, et al., editors, Springer Science+Business Media, LLC, 2nd edition, 2009).

Since typically there are many more potential biomarker values than samples in a training set, care must be used to avoid over-fitting. Over-fitting occurs when a statistical model describes random error or noise instead of the underlying relationship. Over-fitting can be avoided in a variety of way, including, for example, by limiting the number of markers used in developing the classifier, by assuming that the marker responses are independent of one another, by limiting the complexity of the underlying statistical model employed, and by ensuring that the underlying statistical model conforms to the data.

An illustrative example of the development of a diagnostic test using a set of biomarkers includes the application of a naïve Bayes classifier, a simple probabilistic classifier based on Bayes theorem with strict independent treatment of the biomarkers. Each biomarker is described by a class-dependent probability density function (pdf) for the measured RFU values or log RFU (relative fluorescence units) values in each class. The joint pdfs for the set of markers in one class is assumed to be the product of the individual class-dependent pdfs for each biomarker. Training a naïve Bayes classifier in this context amounts to assigning parameters ("parameterization") to characterize the class dependent pdfs. Any underlying model for the class-dependent pdfs may be used, but the model should generally conform to the data observed in the training set.

Specifically, the class-dependent probability of measuring a value x_i for biomarker i in the disease class is written as $p(x_i|d)$ and the overall naïve Bayes probability of observing n markers with values $\underset{\sim}{x}=x_1, x_2, \ldots x_n$) is written as

$$p(\underset{\sim}{x} \mid d) = \prod_{i=1}^{n} p(x_i \mid d)$$

where the individual x_is are the measured biomarker levels in RFU or log RFU. The classification assignment for an unknown is facilitated by calculating the probability of being diseased $p(d|\underset{\sim}{x})$ having measured $\underset{\sim}{x}$ compared to the probability of being disease free (control) $p(c|\underset{\sim}{x})$ for the same measured values. The ratio of these probabilities is computed from the class-dependent pdfs by application of Bayes theorem, i.e.,

$$\frac{p(c \mid \underset{\sim}{x})}{p(d \mid \underset{\sim}{x})} = \frac{p(\underset{\sim}{x} \mid c)(1 - P(d))}{p(\underset{\sim}{x} \mid d)P(d)}$$

where P(d) is the prevalence of the disease in the population appropriate to the test. Taking the logarithm of both sides of this ratio and substituting the naïve Bayes class-dependent probabilities from above gives ln

$$\frac{p(c \mid \underset{\sim}{x})}{p(d \mid \underset{\sim}{x})} = \sum_{i=1}^{n} \ln \frac{p(x_i \mid c)}{p(x_i \mid d)} + \ln \frac{(1 - P(d))}{P(d)}.$$

This form is known as the log likelihood ratio and simply states that the log likelihood of being free of the particular disease versus having the disease and is primarily composed of the sum of individual log likelihood ratios of the n individual biomarkers. In its simplest form, an unknown sample (or, more particularly, the individual from whom the sample was obtained) is classified as being free of the disease if the above ratio is greater than zero and having the disease if the ratio is less than zero.

In one exemplary embodiment, the class-dependent biomarker pdfs $p(x_i|c)$ and $p(x_i|d)$ are assumed to be normal or log-normal distributions in the measured RFU values x_i, i.e.

$$p(x_i \mid c) = \frac{1}{\sqrt{2\pi}\,\sigma_{c,i}} e^{-\frac{(x_i - \mu_{c,i})^2}{2\sigma_{c,i}^2}}$$

with a similar expression for $p(x_i|d)$ with $\mu_{d,i}$ and $\sigma_{d,i}^2$. Parameterization of the model requires estimation of two parameters for each class-dependent pdf, a mean μ and a variance ρ^2, from the training data. This may be accomplished in a number of ways, including, for example, by maximum likelihood estimates, by least-squares, and by any other methods known to one skilled in the art. Substituting the normal distributions for $p(x_i|c)$ and $p(x_i|d)$ into the log-likelihood ratio defined above gives the following expression:

$$\ln \frac{p(c \mid \underset{\sim}{x})}{p(d \mid \underset{\sim}{x})} = \sum_{i=1}^{n} \ln \frac{\sigma_{d,i}}{\sigma_{c,i}} - \frac{1}{2} \sum_{i=1}^{n} \left[\left(\frac{x_i - \mu_{c,i}}{\sigma_{c,i}} \right)^2 - \left(\frac{x_i - \mu_{d,i}}{\sigma_{d,i}} \right)^2 \right] + \ln \frac{(1 - P(d))}{P(d)}.$$

Once a set of μs and σ^ss have been defined for each pdf in each class from the training data and the disease prevalence in the population is specified, the Bayes classifier is fully determined and may be used to classify unknown samples with measured values $\underset{\sim}{x}$.

The performance of the naïve Bayes classifier is dependent upon the number and quality of the biomarkers used to construct and train the classifier. A single biomarker will perform in accordance with its KS-distance (Kolmogorov-Smirnov), as defined in Example 3, below. If a classifier performance metric is defined as the sum of the sensitivity (fraction of true positives, f_{TP}) and specificity (one minus the fraction of false positives, $1-f_{FP}$), a perfect classifier will have a score of two and a random classifier, on average, will have a score of one. Using the definition of the KS-distance, that value x* which maximizes the difference in the cdf functions can be found by solving

$$\frac{\partial KS}{\partial x} = \frac{\partial (cdf_c(x) - cdf_d(x))}{\partial x} = 0$$

for x which leads to $p(x^*|c)=p(x^*|d)$, i.e, the KS distance occurs where the class-dependent pdfs cross. Substituting this value of x* into the expression for the KS-distance yields the following definition for

$$KS = cdf_c(x^*) - cdf_d(x^*) = \int_{-\infty}^{x^*} p(x \mid c)\,dx - \int_{-\infty}^{x^*} p(x \mid d)\,dx =$$
$$1 - \int_{x^*}^{\infty} p(x \mid c)\,dx - \int_{-\infty}^{x^*} p(x \mid d)\,dx = 1 - f_{FP} - f_{FN},$$

the KS distance is one minus the total fraction of errors using a test with a cut-off at x*, essentially a single analyte Bayesian classifier. Since we define a score of sensitivity+specificity=$2-f_{FP}-f_{FN}$, combining the above definition of the KS-distance we see that sensitivity+specificity=1+KS. We select biomarkers with a statistic that is inherently suited for building naïve Bayes classifiers.

The addition of subsequent markers with good KS distances (>0.3, for example) will, in general, improve the classification performance if the subsequently added markers are independent of the first marker. Using the sensitivity plus specificity as a classifier score, it is straightforward to generate many high scoring classifiers with a variation of a greedy algorithm. (A greedy algorithm is any algorithm that follows the problem solving metaheuristic of making the locally optimal choice at each stage with the hope of finding the global optimum.)

The algorithm approach used here is described in detail in Example 4. Briefly, all single analyte classifiers are generated from a table of potential biomarkers and added to a list. Next, all possible additions of a second analyte to each of the stored single analyte classifiers is then performed, saving a predetermined number of the best scoring pairs, say, for example, a thousand, on a new list. All possible three marker classifiers are explored using this new list of the best two-marker classifiers, again saving the best thousand of these. This process continues until the score either plateaus or begins to deteriorate as additional markers are added. Those high scoring classifiers that remain after convergence can be evaluated for the desired performance for an intended use. For example, in one diagnostic application, classifiers with a high sensitivity and modest specificity may be more desirable than modest sensitivity and high specificity. In another diagnostic application, classifiers with a high specificity and a modest sensitivity may be more desirable. The desired level of performance is generally selected based upon a trade-off that must be made between the number of false positives and false negatives that can each be tolerated for the particular diagnostic application. Such trade-offs generally depend on the medical consequences of an error, either false positive or false negative.

Various other techniques are known in the art and may be employed to generate many potential classifiers from a list of biomarkers using a naïve Bayes classifier. In one embodiment, what is referred to as a genetic algorithm can be used to combine different markers using the fitness score as defined above. Genetic algorithms are particularly well suited to exploring a large diverse population of potential classifiers. In another embodiment, so-called ant colony optimization can be used to generate sets of classifiers. Other strategies that are known in the art can also be employed, including, for example, other evolutionary strategies as well as simulated annealing and other stochastic search methods. Metaheuristic methods, such as, for example, harmony search may also be employed.

Exemplary embodiments use any number of the lung cancer biomarkers listed in Table 1, Col. 2 in various

combinations to produce diagnostic tests for detecting lung cancer (see Example 2 for a detailed description of how these biomarkers were identified). In one embodiment, a method for diagnosing lung cancer uses a naïve Bayes classification method in conjunction with any number of the lung cancer biomarkers listed in Table 1, Col. 2. In an illustrative example (Example 3), the simplest test for detecting lung cancer from a population of asymptomatic smokers can be constructed using a single biomarker, for example, SCFsR which is down-regulated in lung cancer with a KS-distance of 0.37 (1+KS=1.37). Using the parameters $\mu_{c,i}$, $\sigma_{c,i}$, $\mu_{d,i}$ and $\sigma_{d,i}$ for SCFsR from Table 41 and the equation for the log-likelihood described above, a diagnostic test with a sensitivity of 63% and specificity of 73% (sensitivity+specificity=1.36) can be produced, see Table 40. The ROC curve for this test is displayed in FIG. **2** and has an AUC of 0.75.

Addition of biomarker HSP90a, for example, with a KS-distance of 0.5, significantly improves the classifier performance to a sensitivity of 76% and specificity of 0.75% (sensitivity+specificity=1.51) and an AUC=0.84. Note that the score for a classifier constructed of two biomarkers is not a simple sum of the KS-distances; KS-distances are not additive when combining biomarkers and it takes many more weak markers to achieve the same level of performance as a strong marker. Adding a third marker, ERBB1, for example, boosts the classifier performance to 78% sensitivity and 83% specificity and AUC=0.87. Adding additional biomarkers, such as, for example, PTN, BTK, CD30, Kallikrein 7, LRIG3, LDH-H1, and PARC, produces a series of lung cancer tests summarized in Table 40 and displayed as a series of ROC curves in FIG. **3**. The score of the classifiers as a function of the number of analytes used in classifier construction is displayed in FIG. **4**. The sensitivity and specificity of this exemplary ten-marker classifier is >87% and the AUC is 0.91.

The markers listed in Table 1, Col. 2 can be combined in many ways to produce classifiers for diagnosing lung cancer. In some embodiments, panels of biomarkers are comprised of different numbers of analytes depending on a specific diagnostic performance criterion that is selected. For example, certain combinations of biomarkers will produce tests that are more sensitive (or more specific) than other combinations.

Once a panel is defined to include a particular set of biomarkers from Table 1, Col. 2 and a classifier is constructed from a set of training data, the definition of the diagnostic test is complete. In one embodiment, the procedure used to classify an unknown sample is outlined in FIG. **1**A. In another embodiment the procedure used to classify an unknown sample is outlined in FIG. **1**B. The biological sample is appropriately diluted and then run in one or more assays to produce the relevant quantitative biomarker levels used for classification. The measured biomarker levels are used as input for the classification method that outputs a classification and an optional score for the sample that reflects the confidence of the class assignment.

Table 1 identifies 61 biomarkers that are useful for diagnosing lung cancer. This is a surprisingly larger number than expected when compared to what is typically found during biomarker discovery efforts and may be attributable to the scale of the described study, which encompassed over 800 proteins measured in hundreds of individual samples, in some cases at concentrations in the low femtomolar range. Presumably, the large number of discovered biomarkers reflects the diverse biochemical pathways implicated in both tumor biology and the body's response to the tumor's presence; each pathway and process involves many proteins. The results show that no single protein of a small group of proteins is uniquely informative about such complex processes; rather, that multiple proteins are involved in relevant processes, such as apoptosis or extracellular matrix repair, for example.

Given the numerous biomarkers identified during the described study, one would expect to be able to derive large numbers of high-performing classifiers that can be used in various diagnostic methods. To test this notion, tens of thousands of classifiers were evaluated using the biomarkers in Table 1. As described in Example 4, many subsets of the biomarkers presented in Table 1 can be combined to generate useful classifiers. By way of example, descriptions are provided for classifiers containing 1, 2, and 3 biomarkers for each of two uses: lung cancer screening of smokers at high risk and diagnosis of individuals that have pulmonary nodules that are detectable by CT. As described in Example 4, all classifiers that were built using the biomarkers in Table 1 perform distinctly better than classifiers that were built using "non-markers".

The performance of classifiers obtained by randomly excluding some of the markers in Table 1, which resulted in smaller subsets from which to build the classifiers, was also tested. As described in Example 4, Part 3, the classifiers that were built from random subsets of the markers in Table 1 performed similarly to optimal classifiers that were built using the full list of markers in Table 1.

The performance of ten-marker classifiers obtained by excluding the "best" individual markers from the ten-marker aggregation was also tested. As described in Example 4, Part 3, classifiers constructed without the "best" markers in Table 1 also performed well. Many subsets of the biomarkers listed in Table 1 performed close to optimally, even after removing the top 15 of the markers listed in the Table. This implies that the performance characteristics of any particular classifier are likely not due to some small core group of biomarkers and that the disease process likely impacts numerous biochemical pathways, which alters the expression level of many proteins.

The results from Example 4 suggest certain possible conclusions: First, the identification of a large number of biomarkers enables their aggregation into a vast number of classifiers that offer similarly high performance. Second, classifiers can be constructed such that particular biomarkers may be substituted for other biomarkers in a manner that reflects the redundancies that undoubtedly pervade the complexities of the underlying disease processes. That is to say, the information about the disease contributed by any individual biomarker identified in Table 1 overlaps with the information contributed by other biomarkers, such that it may be that no particular biomarker or small group of biomarkers in Table 1 must be included in any classifier.

Exemplary embodiments use naïve Bayes classifiers constructed from the data in Tables 38 and 39 to classify an unknown sample. The procedure is outlined in FIGS. **1**A and B. In one embodiment, the biological sample is optionally diluted and run in a multiplexed aptamer assay. The data from the assay are normalized and calibrated as outlined in Example 3, and the resulting biomarker levels are used as input to a Bayes classification scheme. The log-likelihood ratio is computed for each measured biomarker individually and then summed to produce a final classification score, which is also referred to as a diagnostic score. The resulting assignment as well as the overall classification score can be reported. Optionally, the individual log-likelihood risk fac-

tors computed for each biomarker level can be reported as well. The details of the classification score calculation are presented in Example 3.

Kits

Any combination of the biomarkers of Table 1, Col. 2 (as well as additional biomedical information) can be detected using a suitable kit, such as for use in performing the methods disclosed herein. Furthermore, any kit can contain one or more detectable labels as described herein, such as a fluorescent moiety, etc.

In one embodiment, a kit includes (a) one or more capture reagents (such as, for example, at least one aptamer or antibody) for detecting one or more biomarkers in a biological sample, wherein the biomarkers include any of the biomarkers set forth in Table 1, Col. 2, and optionally (b) one or more software or computer program products for classifying the individual from whom the biological sample was obtained as either having or not having lung cancer or for determining the likelihood that the individual has lung cancer, as further described herein. Alternatively, rather than one or more computer program products, one or more instructions for manually performing the above steps by a human can be provided.

The combination of a solid support with a corresponding capture reagent and a signal generating material is referred to herein as a "detection device" or "kit". The kit can also include instructions for using the devices and reagents, handling the sample, and analyzing the data. Further the kit may be used with a computer system or software to analyze and report the result of the analysis of the biological sample.

The kits can also contain one or more reagents (e.g., solubilization buffers, detergents, washes, or buffers) for processing a biological sample. Any of the kits described herein can also include, e.g., buffers, blocking agents, mass spectrometry matrix materials, antibody capture agents, positive control samples, negative control samples, software and information such as protocols, guidance and reference data.

In one aspect, the invention provides kits for the analysis of lung cancer status. The kits include PCR primers for one or more biomarkers selected from Table 1, Col. 2. The kit may further include instructions for use and correlation of the biomarkers with lung cancer. The kit may also include a DNA array containing the complement of one or more of the biomarkers selected from Table 1, Col. 2, reagents, and/or enzymes for amplifying or isolating sample DNA. The kits may include reagents for real-time PCR, for example, TaqMan probes and/or primers, and enzymes.

For example, a kit can comprise (a) reagents comprising at least capture reagent for quantifying one or more biomarkers in a test sample, wherein said biomarkers comprise the biomarkers set forth in Table 1, Col. 2, or any other biomarkers or biomarkers panels described herein, and optionally (b) one or more algorithms or computer programs for performing the steps of comparing the amount of each biomarker quantified in the test sample to one or more predetermined cutoffs and assigning a score for each biomarker quantified based on said comparison, combining the assigned scores for each biomarker quantified to obtain a total score, comparing the total score with a predetermined score, and using said comparison to determine whether an individual has lung cancer. Alternatively, rather than one or more algorithms or computer programs, one or more instructions for manually performing the above steps by a human can be provided.

Computer Methods and Software

Once a biomarker or biomarker panel is selected, a method for diagnosing an individual can comprise the following: 1) collect or otherwise obtain a biological sample; 2) perform an analytical method to detect and measure the biomarker or biomarkers in the panel in the biological sample; 3) perform any data normalization or standardization required for the method used to collect biomarker values; 4) calculate the marker score; 5) combine the marker scores to obtain a total diagnostic score; and 6) report the individual's diagnostic score. In this approach, the diagnostic score may be a single number determined from the sum of all the marker calculations that is compared to a preset threshold value that is an indication of the presence or absence of disease. Or the diagnostic score may be a series of bars that each represent a biomarker value and the pattern of the responses may be compared to a pre-set pattern for determination of the presence or absence of disease.

At least some embodiments of the methods described herein can be implemented with the use of a computer. An example of a computer system **100** is shown in FIG. **6**. With reference to FIG. **6**, system **100** is shown comprised of hardware elements that are electrically coupled via bus **108**, including a processor **101**, input device **102**, output device **103**, storage device **104**, computer-readable storage media reader **105***a*, communications system **106** processing acceleration (e.g., DSP or special-purpose processors) **107** and memory **109**. Computer-readable storage media reader **105***a* is further coupled to computer-readable storage media **105***b*, the combination comprehensively representing remote, local, fixed and/or removable storage devices plus storage media, memory, etc. for temporarily and/or more permanently containing computer-readable information, which can include storage device **104**, memory **109** and/or any other such accessible system **100** resource. System **100** also comprises software elements (shown as being currently located within working memory **191**) including an operating system **192** and other code **193**, such as programs, data and the like.

With respect to FIG. **6**, system **100** has extensive flexibility and configurability. Thus, for example, a single architecture might be utilized to implement one or more servers that can be further configured in accordance with currently desirable protocols, protocol variations, extensions, etc. However, it will be apparent to those skilled in the art that embodiments may well be utilized in accordance with more specific application requirements. For example, one or more system elements might be implemented as sub-elements within a system **100** component (e.g., within communications system **106**). Customized hardware might also be utilized and/or particular elements might be implemented in hardware, software or both. Further, while connection to other computing devices such as network input/output devices (not shown) may be employed, it is to be understood that wired, wireless, modem, and/or other connection or connections to other computing devices might also be utilized.

In one aspect, the system can comprise a database containing features of biomarkers characteristic of lung cancer. The biomarker data (or biomarker information) can be utilized as an input to the computer for use as part of a computer implemented method. The biomarker data can include the data as described herein.

In one aspect, the system further comprises one or more devices for providing input data to the one or more processors.

The system further comprises a memory for storing a data set of ranked data elements.

In another aspect, the device for providing input data comprises a detector for detecting the characteristic of the data element, e.g., such as a mass spectrometer or gene chip reader.

The system additionally may comprise a database management system. User requests or queries can be formatted in an appropriate language understood by the database management system that processes the query to extract the relevant information from the database of training sets.

The system may be connectable to a network to which a network server and one or more clients are connected. The network may be a local area network (LAN) or a wide area network (WAN), as is known in the art. Preferably, the server includes the hardware necessary for running computer program products (e.g., software) to access database data for processing user requests.

The system may include an operating system (e.g., UNIX or Linux) for executing instructions from a database management system. In one aspect, the operating system can operate on a global communications network, such as the internet, and utilize a global communications network server to connect to such a network.

The system may include one or more devices that comprise a graphical display interface comprising interface elements such as buttons, pull down menus, scroll bars, fields for entering text, and the like as are routinely found in graphical user interfaces known in the art. Requests entered on a user interface can be transmitted to an application program in the system for formatting to search for relevant information in one or more of the system databases. Requests or queries entered by a user may be constructed in any suitable database language.

The graphical user interface may be generated by a graphical user interface code as part of the operating system and can be used to input data and/or to display inputted data. The result of processed data can be displayed in the interface, printed on a printer in communication with the system, saved in a memory device, and/or transmitted over the network or can be provided in the form of the computer readable medium.

The system can be in communication with an input device for providing data regarding data elements to the system (e.g., expression values). In one aspect, the input device can include a gene expression profiling system including, e.g., a mass spectrometer, gene chip or array reader, and the like.

The methods and apparatus for analyzing lung cancer biomarker information according to various embodiments may be implemented in any suitable manner, for example, using a computer program operating on a computer system. A conventional computer system comprising a processor and a random access memory, such as a remotely-accessible application server, network server, personal computer or workstation may be used. Additional computer system components may include memory devices or information storage systems, such as a mass storage system and a user interface, for example a conventional monitor, keyboard and tracking device. The computer system may be a stand-alone system or part of a network of computers including a server and one or more databases.

The lung cancer biomarker analysis system can provide functions and operations to complete data analysis, such as data gathering, processing, analysis, reporting and/or diagnosis. For example, in one embodiment, the computer system can execute the computer program that may receive, store, search, analyze, and report information relating to the lung cancer biomarkers. The computer program may comprise multiple modules performing various functions or operations, such as a processing module for processing raw data and generating supplemental data and an analysis module for analyzing raw data and supplemental data to generate a lung cancer status and/or diagnosis. Diagnosing lung cancer status may comprise generating or collecting any other information, including additional biomedical information, regarding the condition of the individual relative to the disease, identifying whether further tests may be desirable, or otherwise evaluating the health status of the individual.

Referring now to FIG. **7**, an example of a method of utilizing a computer in accordance with principles of a disclosed embodiment can be seen. In FIG. **7**, a flowchart **3000** is shown. In block **3004**, biomarker information can be retrieved for an individual. The biomarker information can be retrieved from a computer database, for example, after testing of the individual's biological sample is performed. The biomarker information can comprise biomarker values that each correspond to one of at least N biomarkers selected from a group consisting of the biomarkers provided in Table 1, Col. 2, wherein N=2-61. In block **3008**, a computer can be utilized to classify each of the biomarker values. And, in block **3012**, a determination can be made as to the likelihood that an individual has lung cancer based upon a plurality of classifications. The indication can be output to a display or other indicating device so that it is viewable by a person. Thus, for example, it can be displayed on a display screen of a computer or other output device.

Referring now to FIG. **8**, an alternative method of utilizing a computer in accordance with another embodiment can be illustrated via flowchart **3200**. In block **3204**, a computer can be utilized to retrieve biomarker information for an individual. The biomarker information comprises a biomarker value corresponding to a biomarker selected from the group of biomarkers provided in Table 1, Col. 2. In block **3208**, a classification of the biomarker value can be performed with the computer. And, in block **3212**, an indication can be made as to the likelihood that the individual has lung cancer based upon the classification. The indication can be output to a display or other indicating device so that it is viewable by a person. Thus, for example, it can be displayed on a display screen of a computer or other output device.

Some embodiments described herein can be implemented so as to include a computer program product. A computer program product may include a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer with a database.

As used herein, a "computer program product" refers to an organized set of instructions in the form of natural or programming language statements that are contained on a physical media of any nature (e.g., written, electronic, magnetic, optical or otherwise) and that may be used with a computer or other automated data processing system. Such programming language statements, when executed by a computer or data processing system, cause the computer or data processing system to act in accordance with the particular content of the statements. Computer program products include without limitation: programs in source and object code and/or test or data libraries embedded in a computer readable medium. Furthermore, the computer program product that enables a computer system or data processing equipment device to act in pre-selected ways may be provided in a number of forms, including, but not limited to, original source code, assembly code, object code, machine

language, encrypted or compressed versions of the foregoing and any and all equivalents.

In one aspect, a computer program product is provided for indicating a likelihood of lung cancer. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises biomarker values that each correspond to one of at least N biomarkers in the biological sample selected from the group of biomarkers provided in Table 1, Col. 2, wherein N=2-61; and code that executes a classification method that indicates a lung disease status of the individual as a function of the biomarker values.

In still another aspect, a computer program product is provided for indicating a likelihood of lung cancer. The computer program product includes a computer readable medium embodying program code executable by a processor of a computing device or system, the program code comprising: code that retrieves data attributed to a biological sample from an individual, wherein the data comprises a biomarker value corresponding to a biomarker in the biological sample selected from the group of biomarkers provided in Table 1, Col. 2; and code that executes a classification method that indicates a lung disease status of the individual as a function of the biomarker value.

While various embodiments have been described as methods or apparatuses, it should be understood that embodiments can be implemented through code coupled with a computer, e.g., code resident on a computer or accessible by the computer. For example, software and databases could be utilized to implement many of the methods discussed above. Thus, in addition to embodiments accomplished by hardware, it is also noted that these embodiments can be accomplished through the use of an article of manufacture comprised of a computer usable medium having a computer readable program code embodied therein, which causes the enablement of the functions disclosed in this description. Therefore, it is desired that embodiments also be considered protected by this patent in their program code means as well. Furthermore, the embodiments may be embodied as code stored in a computer-readable memory of virtually any kind including, without limitation, RAM, ROM, magnetic media, optical media, or magneto-optical media. Even more generally, the embodiments could be implemented in software, or in hardware, or any combination thereof including, but not limited to, software running on a general purpose processor, microcode, PLAs, or ASICs.

It is also envisioned that embodiments could be accomplished as computer signals embodied in a carrier wave, as well as signals (e.g., electrical and optical) propagated through a transmission medium. Thus, the various types of information discussed above could be formatted in a structure, such as a data structure, and transmitted as an electrical signal through a transmission medium or stored on a computer readable medium.

It is also noted that many of the structures, materials, and acts recited herein can be recited as means for performing a function or step for performing a function. Therefore, it should be understood that such language is entitled to cover all such structures, materials, or acts disclosed within this specification and their equivalents, including the matter incorporated by reference.

EXAMPLES

The following examples are provided for illustrative purposes only and are not intended to limit the scope of the application as defined by the appended claims. All examples described herein were carried out using standard techniques, which are well known and routine to those of skill in the art. Routine molecular biology techniques described in the following examples can be carried out as described in standard laboratory manuals, such as Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd. ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (2001).

Example 1. Multiplexed Aptamer Analysis of Samples for Lung Cancer Biomarker Selection

This example describes the multiplex aptamer assay used to analyze the samples and controls for the identification of the biomarkers set forth in Table 1, Col. 2 (see FIG. **9**). In this case, the multiplexed analysis utilized 825 aptamers, each unique to a specific target.

In this method, pipette tips were changed for each solution addition.

Also, unless otherwise indicated, most solution transfers and wash additions used the 96-well head of a Beckman Biomek Fx^P. Method steps manually pipetted used a twelve channel P200 Pipetteman (Rainin Instruments, LLC, Oakland, Calif.), unless otherwise indicated. A custom buffer referred to as SB17 was prepared in-house, comprising 40 mM HEPES, 100 mM NaC1, 5 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA at pH7.5. All steps were performed at room temperature unless otherwise indicated.

1. Preparation of Aptamer Stock Solution

For aptamers without a photo-cleavable biotin linker, custom stock aptamer solutions for 10%, 1% and 0.03% serum were prepared at 8× concentration in 1×SB17, 0.05% Tween-20 with appropriate photo-cleavable, biotinylated primers, where the resultant primer concentration was 3 times the relevant aptamer concentration. The primers hybridized to all or part of the corresponding aptamer.

Each of the 3, 8× aptamer solutions were diluted separately 1:4 into 1×SB17, 0.05% Tween-20 (1500 μL of 8× stock into 4500 μL of 1×SB17, 0.05% Tween-20) to achieve a 2× concentration. Each diluted aptamer master mix was then split, 1500 μL each, into 4, 2 mL screw cap tubes and brought to 95° C. for 5 minutes, followed by a 37° C. incubation for 15 minutes. After incubation, the 4, 2 mL tubes corresponding to a particular aptamer master mix were combined into a reagent trough, and 55 μL of a 2× aptamer mix (for all three mixes) was manually pipetted into a 96-well Hybaid plate and the plate foil sealed. The final result was 3, 96-well, foil-sealed Hybaid plates. The individual aptamer concentration ranged from 0.5-4 nM as indicated in Table 28.

2. Assay Sample Preparation

Frozen aliquots of 100% serum, stored at −80° C., were placed in 25° C. water bath for 10 minutes. Thawed samples were placed on ice, gently vortexed (set on 4) for 8 seconds and then replaced on ice.

A 20% sample solution was prepared by transferring 16 μL of sample using a 50 μL 8-channel spanning pipettor into 96-well Hybaid plates, each well containing 64 μL of the appropriate sample diluent at 4° C. (0.8×SB17, 0.05% Tween-20, 2 μM Z-block_2, 0.6 mM $MgCl_2$ for serum). This plate was stored on ice until the next sample dilution steps were initiated.

To commence sample and aptamer equilibration, the 20% sample plate was briefly centrifuged and placed on the Beckman FX where it was mixed by pipetting up and down with the 96-well pipettor. A 2% sample was then prepared by diluting 10 μL of the 20% sample into 90 μL of 1×SB17,

0.05% Tween-20. Next, dilution of 6 μL of the resultant 2% sample into 194 μL of 1×SB17, 0.05% Tween-20 made a 0.06% sample plate. Dilutions were done on the Beckman Biomek Fx^P. After each transfer, the solutions were mixed by pipetting up and down. The 3 sample dilution plates were then transferred to their respective aptamer solutions by adding 55 μL of the sample to 55 μL of the appropriate 2× aptamer mix. The sample and aptamer solutions were mixed on the robot by pipetting up and down.

3. Sample Equilibration Binding

The sample/aptamer plates were foil sealed and placed into a 37° C. incubator for 3.5 hours before proceeding to the Catch 1 step.

4. Preparation of Catch 2 Bead Plate

An 11 mL aliquot of MyOne (Invitrogen Corp., Carlsbad, Calif.) Streptavidin C1 beads was washed 2 times with equal volumes of 20 mM NaOH (5 minute incubation for each wash), 3 times with equal volumes of 1×SB17, 0.05% Tween-20 and resuspended in 11 mL 1×SB17, 0.05% Tween-20. Using a 12-span multichannel pipettor, 50 μL of this solution was manually pipetted into each well of a 96-well Hybaid plate. The plate was then covered with foil and stored at 4° C. for use in the assay.

5. Preparation of Catch 1 Bead Plates

Three 0.45 μm Millipore HV plates (Durapore membrane, Cat# MAHVN4550) were equilibrated with 100 μL of 1×SB17, 0.05% Tween-20 for at least 10 minutes. The equilibration buffer was then filtered through the plate and 133.3 μL of a 7.5% Streptavidin-agarose bead slurry (in 1×SB17, 0.05% Tween-20) was added into each well. To keep the streptavidin-agarose beads suspended while transferring them into the filter plate, the bead solution was manually mixed with a 200 μL, 12-channel pipettor, 15 times. After the beads were distributed across the 3 filter plates, a vacuum was applied to remove the bead supernatant. Finally, the beads were washed in the filter plates with 200 μL 1×SB17, 0.05% Tween-20 and then resuspended in 200 μL 1×SB17, 0.05% Tween-20. The bottoms of the filter plates were blotted and the plates stored for use in the assay.

6. Loading the Cytomat

The cytomat was loaded with all tips, plates, all reagents in troughs (except NHS-biotin reagent which was prepared fresh right before addition to the plates), 3 prepared catch 1 filter plates and 1 prepared MyOne plate.

7. Catch 1

After a 3.5 hour equilibration time, the sample/aptamer plates were removed from the incubator, centrifuged for about 1 minute, foil removed, and placed on the deck of the Beckman Biomek Fx^P. The Beckman Biomek Fx^P program was initiated. All subsequent steps in Catch 1 were performed by the Beckman Biomek Fx^P robot unless otherwise noted. Within the program, the vacuum was applied to the Catch 1 filter plates to remove the bead supernatant. One hundred microliters of each of the 10%, 1% and 0.03% equilibration binding reactions were added to their respective Catch 1 filtration plates, and each plate was mixed using an on-deck orbital shaker at 800 rpm for 10 minutes.

Unbound solution was removed via vacuum filtration. The catch 1 beads were washed with 190 μL of 100 μM biotin in 1×SB17, 0.05% Tween-20 followed by 190 μL of 1×SB17, 0.05% Tween-20 by dispensing the solution and immediately drawing a vacuum to filter the solution through the plate.

Next, 190 μL 1×SB17, 0.05% Tween-20 was added to the Catch 1 plates. Plates were blotted to remove droplets using an on-deck blot station and then incubated with orbital shakers at 800 rpm for 10 minutes at 25° C.

The robot removed this wash via vacuum filtration and blotted the bottom of the filter plate to remove droplets using the on-deck blot station.

8. Tagging

A NHS-PEO4-biotin aliquot was thawed at 37° C. for 6 minutes and then diluted 1:100 with tagging buffer (SB17 at pH=7.25 0.05% Tween-20). The NHS-PEO4-biotin reagent was dissolved at 100 mM concentration in anhydrous DMSO and had been stored frozen at −20° C. Upon a robot prompt, the diluted NHS-PEO4-biotin reagent was manually added to an on-deck trough and the robot program was manually re-initiated to dispense 100 μL of the NHS-PEO4-biotin into each well of each Catch 1 filter plate. This solution was allowed to incubate with Catch 1 beads shaking at 800 rpm for 5 minutes on the obital shakers.

9. Kinetic Challenge and Photo-Cleavage

The tagging reaction was quenched by the addition of 150 μL of 20 mM glycine in 1×SB17, 0.05% Tween-20 to the Catch 1 plates while still containing the NHS tag. The plates were then incubated for 1 minute on orbital shakers at 800 rpm. The NHS-tag/glycine solution was removed via vacuum filtration. Next, 190 μL 20 mM glycine (1×SB17, 0.05% Tween-20) was added to each plate and incubated for 1 minute on orbital shakers at 800 rpm before removal by vacuum filtration.

190 μL of 1×SB17, 0.05% Tween-20 was added to each plate and removed by vacuum filtration.

The wells of the Catch 1 plates were subsequently washed three times by adding 190 μL 1×SB17, 0.05% Tween-20, placing the plates on orbital shakers for 1 minute at 800 rpm followed by vacuum filtration. After the last wash the plates were placed on top of a 1 mL deep-well plate and removed from the deck. The Catch 1 plates were centrifuged at 1000 rpm for 1 minute to remove as much extraneous volume from the agarose beads before elution as possible.

The plates were placed back onto the Beckman Biomek Fx^P and 85 μL of 10 mM $Dx50_4$ in 1×SB17, 0.05% Tween-20 was added to each well of the filter plates.

The filter plates were removed from the deck, placed onto a Variomag Thermoshaker (Thermo Fisher Scientific, Inc., Waltham, Mass.) under the BlackRay (Ted Pella, Inc., Redding, Calif.) light sources, and irradiated for 10 minutes while shaking at 800 rpm.

The photocleaved solutions were sequentially eluted from each Catch 1 plate into a common deep well plate by first placing the 10% Catch 1 filter plate on top of a 1 mL deep-well plate and centrifuging at 1000 rpm for 1 minute. The 1% and 0.03% catch 1 plates were then sequentially centrifuged into the same deep well plate.

10. Catch 2 Bead Capture

The 1 mL deep well block containing the combined eluates of catch 1 was placed on the deck of the Beckman Biomek Fx^P for catch 2.

The robot transferred all of the photo-cleaved eluate from the 1 mL deep-well plate onto the Hybaid plate containing the previously prepared catch 2 MyOne magnetic beads (after removal of the MyOne buffer via magnetic separation).

The solution was incubated while shaking at 1350 rpm for 5 minutes at 25° C. on a Variomag Thermoshaker (Thermo Fisher Scientific, Inc., Waltham, Mass.).

The robot transferred the plate to the on deck magnetic separator station. The plate was incubated on the magnet for 90 seconds before removal and discarding of the supernatant.

11. 37° C. 30% Glycerol Washes

The catch 2 plate was moved to the on-deck thermal shaker and 75 μL of 1×SB17, 0.05% Tween-20 was transferred to each well. The plate was mixed for 1 minute at 1350 rpm and 37° C. to resuspend and warm the beads. To each well of the catch 2 plate, 75 μL of 60% glycerol at 37° C. was transferred and the plate continued to mix for another minute at 1350 rpm and 37° C. The robot transferred the plate to the 37° C. magnetic separator where it was incubated on the magnet for 2 minutes and then the robot removed and discarded the supernatant. These washes were repeated two more times.

After removal of the third 30% glycerol wash from the catch 2 beads, 150 μL of 1×SB17, 0.05% Tween-20 was added to each well and incubated at 37° C., shaking at 1350 rpm for 1 minute, before removal by magnetic separation on the 37° C. magnet.

The catch 2 beads were washed a final time using 150 μL 1×SB19, 0.05% Tween-20 with incubation for 1 minute while shaking at 1350 rpm, prior to magnetic separation.

12. Catch 2 Bead Elution and Neutralization

The aptamers were eluted from catch 2 beads by adding 105 μL of 100 mM CAPSO with 1 M NaCl, 0.05% Tween-20 to each well. The beads were incubated with this solution with shaking at 1300 rpm for 5 minutes.

The catch 2 plate was then placed onto the magnetic separator for 90 seconds prior to transferring 90 μL of the eluate to a new 96-well plate containing 10 μL of 500 mM HCl, 500 mM HEPES, 0.05% Tween-20 in each well. After transfer, the solution was mixed robotically by pipetting 90 μL up and down five times.

13. Hybridization

The Beckman Biomek Fx^P transferred 20 μL of the neutralized catch 2 eluate to a fresh Hybaid plate, and 5 μL of 10× Agilent Block, containing a 10× spike of hybridization controls, was added to each well. Next, 25 μL of 2× Agilent Hybridization buffer was manually pipetted to the each well of the plate containing the neutralized samples and blocking buffer and the solution was mixed by manually pipetting 25 μL up and down 15 times slowly to avoid extensive bubble formation. The plate was spun at 1000 rpm for 1 minute.

A gasket slide was placed into an Agilent hybridization chamber and 40 μL of each of the samples containing hybridization and blocking solution was manually pipetted into each gasket. An 8-channel variable spanning pipettor was used in a manner intended to minimize bubble formation. Custom Agilent microarray slides (Agilent Technologies, Inc., Santa Clara, Calif.), with their Number Barcode facing up, were then slowly lowered onto the gasket slides (see Agilent manual for detailed description).

The top of the hybridization chambers were placed onto the slide/backing sandwich and clamping brackets slid over the whole assembly. These assemblies were tightly clamped by turning the screws securely.

Each slide/backing slide sandwich was visually inspected to assure the solution bubble could move freely within the sample. If the bubble did not move freely the hybridization chamber assembly was gently tapped to disengage bubbles lodged near the gasket.

The assembled hybridization chambers were incubated in an Agilent hybridization oven for 19 hours at 60° C. rotating at 20 rpm.

14. Post Hybridization Washing

Approximately 400 mL Agilent Wash Buffer 1 was placed into each of two separate glass staining dishes. One of the staining dishes was placed on a magnetic stir plate and a slide rack and stir bar were placed into the buffer.

A staining dish for Agilent Wash 2 was prepared by placing a stir bar into an empty glass staining dish.

A fourth glass staining dish was set aside for the final acetonitrile wash.

Each of six hybridization chambers was disassembled. One-by-one, the slide/backing sandwich was removed from its hybridization chamber and submerged into the staining dish containing Wash 1. The slide/backing sandwich was pried apart using a pair of tweezers, while still submerging the microarray slide. The slide was quickly transferred into the slide rack in the Wash 1 staining dish on the magnetic stir plate.

The slide rack was gently raised and lowered 5 times. The magnetic stirrer was turned on at a low setting and the slides incubated for 5 minutes.

When one minute was remaining for Wash 1, Wash Buffer 2 pre-warmed to 37° C. in an incubator was added to the second prepared staining dish. The slide rack was quickly transferred to Wash Buffer 2 and any excess buffer on the bottom of the rack was removed by scraping it on the top of the stain dish. The slide rack was gently raised and lowered 5 times. The magnetic stirrer was turned on at a low setting and the slides incubated for 5 minutes.

The slide rack was slowly pulled out of Wash 2, taking approximately 15 seconds to remove the slides from the solution.

With one minute remaining in Wash 2 acetonitrile (ACN) was added to the fourth staining dish. The slide rack was transferred to the acetonitrile stain dish. The slide rack was gently raised and lowered 5 times. The magnetic stirrer was turned on at a low setting and the slides incubated for 5 minutes.

The slide rack was slowly pulled out of the ACN stain dish and placed on an absorbent towel. The bottom edges of the slides were quickly dried and the slide was placed into a clean slide box.

15. Microarray Imaging

The microarray slides were placed into Agilent scanner slide holders and loaded into the Agilent Microarray scanner according to the manufacturer's instructions.

The slides were imaged in the Cy3-channel at 5 μm resolution at the 100% PMT setting and the XRD option enabled at 0.05. The resulting tiff images were processed using Agilent feature extraction software version 10.5.

Example 2. Biomarker Identification

The identification of potential lung cancer biomarkers was performed for three different diagnostic applications, diagnosis of suspicious nodules from a CT scan, screening of asymptomatic smokers for lung cancer, and diagnosing an individual with lung cancer. Serum samples were collected from four different sites in support of these three applications and include 247 NSCLC cases, 420 benign nodule controls and 352 asymptomatic smoker controls. Table 29 summarizes the site sample information. The multiplexed aptamer affinity assay as described in Example 1 was used to measure and report the RFU value for 825 analytes in each of these 1019 samples. Since the serum samples were obtained from four independent studies and sites under similar but different protocols, an examination of site differences prior to the analysis for biomarkers discovery was performed. Each of the three populations, benign nodule, asymptomatic smokers, and NSCLC, were separately compared between sites by generating within-site, class-depen-

dent cumulative distribution functions (cdfs) for each of the 825 analytes. The KS-test was then applied to each analyte between all site pairs within a common class to identify those analytes that differed not by class but rather by site. In all site comparisons among the three classes, statistically significant site-dependent differences were observed. The KS-distance (Kolmogorov-Smirnov statistic) between values from two sets of samples is a non parametric measurement of the extent to which the empirical distribution of the values from one set (Set A) differs from the distribution of values from the other set (Set B). For any value of a threshold T some proportion of the values from Set A will be less than T, and some proportion of the values from Set B will be less than T. The KS-distance measures the maximum (unsigned) difference between the proportion of the values from the two sets for any choice of T.

Such site-dependent effects tend to obscure the ability to identify specific control-disease differences. In order to minimize such effects and identify key disease dependent biomarkers, three distinct strategies were employed for biomarker discovery, namely (1) aggregated class-dependent cdfs across sites, (2) comparison of within-site class-dependent cdfs, and (3) blending methods (1) with (2). Details of these three methodologies and their results follow.

These three sets of potential biomarkers can be used to build classifiers that assign samples to either a control or disease group. In fact, many such classifiers were produced from these sets of biomarkers and the frequency with which any biomarker was used in good scoring classifiers determined Those biomarkers that occurred most frequently among the top scoring classifiers were the most useful for creating a diagnostic test. In this example, Bayesian classifiers were used to explore the classification space but many other supervised learning techniques may be employed for this purpose. The scoring fitness of any individual classifier was gauged by summing the sensitivity and specificity of the classifier at the Bayesian surface assuming a disease prevalence of 0.5. This scoring metric varies from zero to two, with two being an error-free classifier. The details of constructing a Bayesian classifier from biomarker population measurements are described in Example 3.

By aggregating the class-dependent samples across all sites in method (1), those analyte measurements that showed large site-to-site variation, on average, failed to exhibit class-dependent differences due to the large site-to-site differences. Such analytes were automatically removed from further analysis. However, those analytes that did show class-dependent differences across the sites are fairly robust biomarkers that were relatively insensitive to sample collection and sample handling variability. KS-distances were computed for all analytes using the class-dependent cdfs aggregated across all sites. Using a KS-distance threshold of 0.3 led to the identification of sixty five potential biomarkers for the benign nodule-NSCLC comparison and eighty three for the smoker-NSCLC comparison.

Using the sixty-five analytes exceeding the KS-distance threshold, a total of 282 10-analyte classifiers were found with a score of 1.7 or better (>85% sensitivity and >85% specificity, on average) for diagnosing NSCLC from a control group with benign nodules. From this set of classifiers, a total of nineteen biomarkers were found to be present in 10.0% or more of the high scoring classifiers. Table 30 provides a list of these potential biomarkers and FIG. **10** is a frequency plot for the identified biomarkers.

For the diagnosis of NSCLC from a group of asymptomatic smokers, a total of 1249 classifiers, each comprised of ten analytes, were found with a score of 1.7 or better using the eighty three potential biomarkers identified above. A total of twenty one analytes appear in this set of classifiers 10.0% or more. Table 31 provides a list of these biomarkers and FIG. **11** is a frequency plot for the identified biomarkers. This completed the biomarker identification using method (1).

Method (2) focused on consistency of potential biomarker changes between the control and case groups (nodules and smokers with lung cancer) among the individual sites. The class-dependent cdfs were constructed for all analytes within each site separately and from these cdfs the KS-distances were computed to identify potential biomarkers. Here, an analyte must have a KS-distance greater than some threshold in all the sites to be considered a potential biomarker. For the benign nodule versus NSCLC comparisons, a threshold of 0.3 yielded eleven analytes with consistent differences between case and control among the sites. Lowering the threshold to 0.275 for the KS-distance yielded nineteen analytes. Using these nineteen analytes to build potential 10-analyte Bayesian classifiers, there were 2897 classifiers that had a score of 1.6 or better. All nineteen analytes occurred with a frequency greater than 10% and are presented in Table 32 and FIG. **12**.

For the asymptomatic smoker group versus the NSCLC group, a similar analysis yielded thirty-three analytes with KS-distances greater than 0.3 among all the sites. Building ten-analyte classifiers from this set of potential biomarkers yielded nineteen biomarkers with frequencies >10.0% in 1249 classifiers scoring 1.7 or higher. These analytes are displayed in Table 33 and FIG. **13**.

Finally, by combining a core group of biomarkers identified by method (2) with those additional potential biomarkers identified in method (1) a set of classifiers was produced from this blended set of potential biomarkers. For the benign nodule diagnostic, the core group of biomarkers included those six analytes with a frequency >0.5. These six analytes were used to seed a Bayesian classifier to which additional markers were added up to a total of fifteen proteins. For a classification score >1.65, a total of 1316 Bayesian classifiers were built from this core. Twenty five potential biomarkers were identified from this set of classifiers using a frequency cut-off of 10%. These analytes are displayed in Table 34 and FIG. **14** is a frequency plot for the identified biomarkers. A similar analysis for the asymptomatic smoker and NSCLC groups identifies twenty six potential biomarkers from 1508 fifteen protein classifiers with scores >1.7 starting with a core from method (2) of seven proteins. Table 35 displays these results and FIG. **15** is a frequency plot for the identified biomarkers.

Biomarkers from FIGS. **10-15** were combined to generate a final list of biomarkers for lung cancer in Table 36. Table 37 includes a dissociation constant for the aptamer used to identify the biomarker, the limit of quantification for the marker in the multiplex aptamer assay, and whether the marker was up-regulated or down-regulated in the diseased population relative to the control population.

Example 3. Naïve Bayesian Classification for Lung Cancer

From the list of biomarkers identified as useful for discriminating between NSCLC and benign nodules, a panel of ten biomarkers was selected and a naïve Bayes classifier was constructed, see Table 41. The class-dependent probability density functions (pdfs), $p(x_i|c)$ and $p(x_i|d)$, where x_i is the log of the measured RFU value for biomarker i, and c and d refer to the control and disease populations, were modeled

as normal distribution functions characterized by a mean μ and variance σ^2. The parameters for pdfs of the ten biomarkers are listed in Table 41 and an example of the raw data along with the model fit to a normal pdf is displayed in FIG. **5**. The underlying assumption appears to fit the data quite well as evidenced by FIG. **5**.

The naïve Bayes classification for such a model is given by the following equation, where P(d) is the prevalence of the disease in the population

$$\ln\frac{p(c\mid \underset{\sim}{x})}{p(d\mid \underset{\sim}{x})}=\sum_{i=1}^{n}\left(\ln\frac{\sigma_{d,i}}{\sigma_{c,i}}-\frac{1}{2}\left[\left(\frac{x_i-\mu_{c,i}}{\sigma_{c,i}}\right)^2-\left(\frac{x_i-\mu_{d,i}}{\sigma_{d,i}}\right)^2\right]\right)+\ln\frac{(1-P(d))}{P(d)}$$

appropriate to the test and n=10 here. Each of the terms in the summation is a log-likelihood ratio for an individual marker and the total log-likelihood ratio of a sample $\underset{\sim}{x}$ being free from the disease of interest (i.e. in this case, NSCLC) versus having the disease is simply the sum of these individual terms plus a term that accounts for the prevalence of the disease. For simplicity, we assume P(d)=0.5 so that

$$\ln\frac{(1-P(d))}{P(d)}=0.$$

Given an unknown sample measurement in log(RFU) for each of the ten biomarkers of $\underset{\sim}{x}$=(3.13, 4.13, 4.48, 4.58, 3.78, 2.55, 3.02, 3.49, 2.92, 4.44), the calculation of the classification is detailed in Table 42. The individual components comprising the log likelihood ratio for control versus disease class are tabulated and can be computed from the parameters in Table 41 and the values of $\underset{\sim}{x}$. The sum of the individual log likelihood ratios is 5.77, or a likelihood of being free from the disease versus having the disease of 321:1, where likelihood=$e^{5.77}$=321. The first two biomarker values have likelihoods more consistent with the disease group (log likelihood <0) but the remaining eight biomarkers are all consistently found to favor the control group, the largest by a factor of 3:1. Multiplying the likelihoods together gives the same results as that shown above; a likelihood of 321:1 that the unknown sample is free from the disease. In fact, this sample came from the control population in the training set.

Example 4. Greedy Algorithm for Selecting Biomarker Panels for Classifiers

Part 1

This example describes the selection of biomarkers from Table 1 to form panels that can be used as classifiers in any of the methods described herein. Subsets of the biomarkers in Table 1 were selected to construct classifiers with good performance. This method was also used to determine which potential markers were included as biomarkers in Example 2.

The measure of classifier performance used here is the sum of the sensitivity and specificity; a performance of 1.0 is the baseline expectation for a random (coin toss) classifier, a classifier worse than random would score between 0.0 and 1.0, a classifier with better than random performance would score between 1.0 and 2.0. A perfect classifier with no errors would have a sensitivity of 1.0 and a specificity of 1.0, therefore a performance of 2.0 (1.0+1.0). One can apply the methods described in Example 4 to other common measures of performance such as area under the ROC curve, the F-measure, or the product of sensitivity and specificity. Specifically one might want to treat specificity and specificity with differing weight, so as to select those classifiers which perform with higher specificity at the expense of some sensitivity, or to select those classifiers which perform with higher sensitivity at the expense of some specificity. Since the method described here only involves a measure of "performance", any weighting scheme which results in a single performance measure can be used. Different applications will have different benefits for true positive and true negative findings, and also different costs associated with false positive findings from false negative findings. For example, screening asymptomatic smokers and the differential diagnosis of benign nodules found on CT will not in general have the same optimal trade-off between specificity and sensitivity. The different demands of the two tests will in general require setting different weighting to positive and negative misclassifications, reflected in the performance measure. Changing the performance measure will in general change the exact subset of markers selected from Table 1, Col. 2 for a given set of data.

For the Bayesian approach to the discrimination of lung cancer samples from control samples described in Example 3, the classifier was completely parameterized by the distributions of biomarkers in the disease and benign training samples, and the list of biomarkers was chosen from Table 1; that is to say, the subset of markers chosen for inclusion determined a classifier in a one-to-one manner given a set of training data.

The greedy method employed here was used to search for the optimal subset of markers from Table 1. For small numbers of markers or classifiers with relatively few markers, every possible subset of markers was enumerated and evaluated in terms of the performance of the classifier constructed with that particular set of markers (see Example 4, Part 2). (This approach is well known in the field of statistics as "best subset selection"; see, e.g., Hastie et al, supra). However, for the classifiers described herein, the number of combinations of multiple markers can be very large, and it was not feasible to evaluate every possible set of 10 markers, for example, from the list of 40 markers (Table 39) (i.e., 847,660,528 combinations). Because of the impracticality of searching through every subset of markers, the single optimal subset may not be found; however, by using this approach, many excellent subsets were found, and, in many cases, any of these subsets may represent an optimal one.

Instead of evaluating every possible set of markers, a "greedy" forward stepwise approach may be followed (see, e.g., Dabney A R, Storey J D (2007) Optimality Driven Nearest Centroid Classification from Genomic Data. PLoS ONE 2(10): e1002. doi:10.1371/journal.pone.0001002). Using this method, a classifier is started with the best single marker (based on KS-distance for the individual markers) and is grown at each step by trying, in turn, each member of a marker list that is not currently a member of the set of markers in the classifier. The one marker which scores best in combination with the existing classifier is added to the classifier. This is repeated until no further improvement in performance is achieved. Unfortunately, this approach may miss valuable combinations of markers for which some of the individual markers are not all chosen before the process stops.

The greedy procedure used here was an elaboration of the preceding forward stepwise approach, in that, to broaden the

search, rather than keeping just a single candidate classifier (marker subset) at each step, a list of candidate classifiers was kept. The list was seeded with every single marker subset (using every marker in the table on its own). The list was expanded in steps by deriving new classifiers (marker subsets) from the ones currently on the list and adding them to the list. Each marker subset currently on the list was extended by adding any marker from Table 1 not already part of that classifier, and which would not, on its addition to the subset, duplicate an existing subset (these are termed "permissible markers"). Every existing marker subset was extended by every permissible marker from the list. Clearly, such a process would eventually generate every possible subset, and the list would run out of space. Therefore, all the generated classifiers were kept only while the list was less than some predetermined size (often enough to hold all three marker subsets). Once the list reached the predetermined size limit, it became elitist; that is, only those classifiers which showed a certain level of performance were kept on the list, and the others fell off the end of the list and were lost. This was achieved by keeping the list sorted in order of classifier performance; new classifiers which were at least as good as the worst classifier currently on the list were inserted, forcing the expulsion of the current bottom underachiever. One further implementation detail is that the list was completely replaced on each generational step; therefore, every classifier on the list had the same number of markers, and at each step the number of markers per classifier grew by one.

Since this method produced a list of candidate classifiers using different combinations of markers, one may ask if the classifiers can be combined in order to avoid errors which might be made by the best single classifier, or by minority groups of the best classifiers. Such "ensemble" and "committee of experts" methods are well known in the fields of statistical and machine learning and include, for example, "Averaging", "Voting", "Stacking", "Bagging" and "Boosting" (see, e.g., Hastie et al., supra). These combinations of simple classifiers provide a method for reducing the variance in the classifications due to noise in any particular set of markers by including several different classifiers and therefore information from a larger set of the markers from the biomarker table, effectively averaging between the classifiers. An example of the usefulness of this approach is that it can prevent outliers in a single marker from adversely affecting the classification of a single sample. The requirement to measure a larger number of signals may be impractical in conventional one marker at a time antibody assays but has no downside for a fully multiplexed aptamer assay. Techniques such as these benefit from a more extensive table of biomarkers and use the multiple sources of information concerning the disease processes to provide a more robust classification.

Part 2

The biomarkers selected in Table 1 gave rise to classifiers which perform better than classifiers built with "non-markers" (i.e., proteins having signals that did not meet the criteria for inclusion in Table 1 (as described in Example 2)).

For classifiers containing only one, two, and three markers, all possible classifiers obtained using the biomarkers in Table 1 were enumerated and examined for the distribution of performance compared to classifiers built from a similar table of randomly selected non-markers signals.

In FIG. **17** and FIG. **18**, the sum of the sensitivity and specificity was used as the measure of performance; a performance of 1.0 is the baseline expectation for a random (coin toss) classifier. The histogram of classifier performance was compared with the histogram of performance from a similar exhaustive enumeration of classifiers built from a "non-marker" table of 40 non-marker signals; the 40 signals were randomly chosen from 400 aptamers that did not demonstrate differential signaling between control and disease populations (KS-distance<1.4).

FIG. **17** shows histograms of the performance of all possible one, two, and three-marker classifiers built from the biomarker parameters in Table 39 for biomarkers that can discriminate between benign nodules and NSCLC and compares these classifiers with all possible one, two, and three-marker classifiers built using the 40 "non-marker" aptamer RFU signals. FIG. **17**A shows the histograms of single marker classifier performance, FIG. **17**B shows the histogram of two marker classifier performance, and FIG. **17**C shows the histogram of three marker classifier performance.

In FIG. **17**, the solid lines represent the histograms of the classifier performance of all one, two, and three-marker classifiers using the biomarker data for benign nodules and NSCLC in Table 39. The dotted lines are the histograms of the classifier performance of all one, two, and three-marker classifiers using the data for benign nodules and NSCLC but using the set of random non-marker signals.

FIG. **18** shows histograms of the performance of all possible one, two, and three-marker classifiers built from the biomarker parameters in Table 38 for biomarkers that can discriminate between asymptomatic smokers and NSCLC and compares these with all possible one, two, and three-marker classifiers built using 40 "non-marker" aptamer RFU signals. FIG. **18**A shows the histograms of single marker classifier performance, FIG. **18**B shows the histogram of two marker classifier performance, and FIG. **18**C shows the histogram of three marker classifier performance.

In FIG. **18**, the solid lines represent the histograms of the classifier performance of all one, two, and three-marker classifiers using the biomarker parameters for asymptomatic smokers and NSCLC in Table 38. The dotted lines are the histograms of the classifier performance of all one, two, and three-marker classifiers using the data for asymptomatic smokers and NSCLC but using the set of random non-marker signals.

The classifiers built from the markers listed in Table 1 form a distinct histogram, well separated from the classifiers built with signals from the "non-markers" for all one-marker, two-marker, and three-marker comparisons. The performance and AUC score of the classifiers built from the biomarkers in Table 1 also increase faster with the number of markers than do the classifiers built from the non-markers, the separation increases between the marker and non-marker classifiers as the number of markers per classifier increases. All classifiers built using the biomarkers listed in Tables 38 and 39 perform distinctly better than classifiers built using the "non-markers".

Part 3

To test whether a core subset of markers accounted for the good performance of the classifiers, half of the markers were randomly dropped from the lists of biomarkers in Tables 38 and 39. The performance, as measured by sensitivity plus specificity, of classifiers for distinguishing benign nodules from malignant nodules dropped slightly by 0.07 (from 1.74 to 1.67), and the performance of classifiers for distinguishing smokers who had cancer from those who did not also dropped slightly by 0.06 (from 1.76 to 1.70). The implication of the performance characteristics of subsets of the biomarker table is that multiple subsets of the listed bio-

markers are effective in building a diagnostic test, and no particular core subset of markers dictates classifier performance.

In the light of these results, classifiers that excluded the best markers from Tables 38 and 39 were tested. FIG. **19** compares the performance of classifiers built with the full list of biomarkers in Tables 38 and 39 with the performance of classifiers built with a set of biomarkers from Tables 38 and 39 excluding top ranked markers.

FIG. **19** demonstrates that classifiers constructed without the best markers perform well, implying that the performance of the classifiers was not due to some small core group of markers and that the changes in the underlying processes associated with disease are reflected in the activities of many proteins. Many subsets of the biomarkers in Table 1 performed close to optimally, even after removing the top 15 of the 40 markers from Table 1.

FIG. **19**A shows the effect on classifiers for discriminating benign nodules from NSCLC built with 2 to 10 markers. Even after dropping the 15 top-ranked markers (ranked by KS-distance) from Table 39, the benign nodule vs. NSCLC performance increased with the number of markers selected from the table to reach over 1.65 (Sensitivity+Specificity).

FIG. **19**B shows the effect on classifiers for discriminating asymptomatic smokers from NSCLC built with 2 to 10 markers. Even after dropping the 15 top-ranked markers (ranked by KS-distance) from Table 38, the asymptomatic smokers vs. NSCLC performance increased with the number of markers selected from the table to reach over 1.7 (Sensitivity+Specificity), and closely approached the performance of the best classifier selected from the full list of biomarkers in Table 38.

Finally, FIG. **20** shows how the ROC performance of typical classifiers constructed from the list of parameters in Tables 38 and 39 according to Example 3. FIG. **20**A shows the model performance from assuming the independence of markers as in Example 3, and FIG. **20**B shows the actual ROC curves using the assay data set used to generate the parameters in Tables 38 and 39. It can be seen that the performance for a given number of selected markers was qualitatively in agreement, and that quantitative agreement degraded as the number of markers increases. (This is consistent with the notion that the information contributed by any particular biomarker concerning the disease processes is redundant with the information contributed by other biomarkers provided in Tables 38 and 39). FIG. **20** thus demonstrates that Tables 38 and 39 in combination with the methods described in Example 3 enable the construction and evaluation of a great many classifiers useful for the discrimination of NSCLC from benign nodules and the discrimination of asymptomatic smokers who have NSCLC from those who do not have NSCLC.

Example 5. Aptamer Specificity Demonstration in a Pull-down Assay

The final readout on the multiplex assay is based on the amount of aptamer recovered after the successive capture steps in the assay. The multiplex assay is based on the premise that the amount of aptamer recovered at the end of the assay is proportional to the amount of protein in the original complex mixture (e.g., plasma). In order to demonstrate that this signal is indeed derived from the intended analyte rather than from non-specifically bound proteins in plasma, we developed a gel-based pull-down assay in plasma. This assay can be used to visually demonstrate that a desired protein is in fact pulled out from plasma after equilibration with an aptamer as well as to demonstrate that aptamers bound to their intended protein targets can survive as a complex through the kinetic challenge steps in the assay. In the experiments described in this example, recovery of protein at the end of this pull-down assay requires that the protein remain non-covalently bound to the aptamer for nearly two hours after equilibration. Importantly, in this example we also provide evidence that non-specifically bound proteins dissociate during these steps and do not contribute significantly to the final signal. It should be noted that the pull-down procedure described in this example includes all of the key steps in the multiplex assay described above.

A. Plasma Pull-Down Assay

Plasma samples were prepared by diluting 50 μL EDTA-plasma to 100 μL in SB18 with 0.05% Tween-20 (SB18T) and 2 μM Z-Block. The plasma solution was equilibrated with 10 pmoles of a PBDC-aptamer in a final volume of 150 μL for 2 hours at 37° C. After equilibration, complexes and unbound aptamer were captured with 133 μL of a 7.5% Streptavidin-agarose bead slurry by incubating with shaking for 5 minutes at RT in a Durapore filter plate. The samples bound to beads were washed with biotin and with buffer under vacuum as described in Example 1. After washing, bound proteins were labeled with 0.5 mM NHS-S-S-biotin, 0.25 mM NHS-Alexa647 in the biotin diluent for 5 minutes with shaking at RT. This staining step allows biotinylation for capture of protein on streptavidin beads as well as highly sensitive staining for detection on a gel. The samples were washed with glycine and with buffer as described in Example 1. Aptamers were released from the beads by photocleavage using a Black Ray light source for 10 minutes with shaking at RT. At this point, the biotinylated proteins were captured on 0.5 mg MyOne Streptavidin beads by shaking for 5 minutes at RT. This step will capture proteins bound to aptamers as well as proteins that may have dissociated from aptamers since the initial equilibration. The beads were washed as described in Example 1. Proteins were eluted from the MyOne Streptavidin beads by incubating with 50 mM DTT in SB17T for 25 minutes at 37° C. with shaking. The eluate was then transferred to MyOne beads coated with a sequence complimentary to the 3' fixed region of the aptamer and incubated for 25 minutes at 37° C. with shaking. This step captures all of the remaining aptamer. The beads were washed 2× with 100 μL SB17T for 1 minute and 1× with 100 μL SB19T for 1 minute. Aptamer was eluted from these final beads by incubating with 45 μL 20 mM NaOH for 2 minutes with shaking to disrupt the hybridized strands. 40 μL of this eluate was neutralized with 10 μL 80 mM HCl containing 0.05% Tween-20. Aliquots representing 5% of the eluate from the first set of beads (representing all plasma proteins bound to the aptamer) and 20% of the eluate from the final set of beads (representing all plasma proteins remaining bound at the end of our clinical assay) were run on a NuPAGE 4-12% Bis-Tris gel (Invitrogen) under reducing and denaturing conditions. Gels were imaged on an Alpha Innotech FluorChem Q scanner in the Cy5 channel to image the proteins.

B. Pull-down gels for aptamers were selected against LBP (~1×10^{-7} M in plasma, polypeptide MW ~60 kDa), C9 (~1×10^{-6} M in plasma, polypeptide MW ~60 kDa), and IgM (~9×10^{-6} M in plasma, MW ~70 kDa and 23 kDa), respectively. (See FIG. **16**).

For each gel, lane 1 is the eluate from the Streptavidin-agarose beads, lane 2 is the final eluate, and lane 3 is a MW marker lane (major bands are at 110, 50, 30, 15, and 3.5 kDa from top to bottom). It is evident from these gels that there

is a small amount non-specific binding of plasma proteins in the initial equilibration, but only the target remains after performing the capture steps of the assay. It is clear that the single aptamer reagent is sufficient to capture its intended analyte with no up-front depletion or fractionation of the plasma. The amount of remaining aptamer after these steps is then proportional to the amount of the analyte in the initial sample.

The foregoing embodiments and examples are intended only as examples. No particular embodiment, example, or element of a particular embodiment or example is to be construed as a critical, required, or essential element or feature of any of the claims. Further, no element described herein is required for the practice of the appended claims unless expressly described as "essential" or "critical." Various alterations, modifications, substitutions, and other variations can be made to the disclosed embodiments without departing from the scope of the present application, which is defined by the appended claims. The specification, including the figures and examples, is to be regarded in an illustrative manner, rather than a restrictive one, and all such modifications and substitutions are intended to be included within the scope of the application. Accordingly, the scope of the application should be determined by the appended claims and their legal equivalents, rather than by the examples given above. For example, steps recited in any of the method or process claims may be executed in any feasible order and are not limited to an order presented in any of the embodiments, the examples, or the claims. Further, in any of the aforementioned methods, one or more biomarkers of Table 1 can be specifically excluded either as an individual biomarker or as a biomarker from any panel.

TABLE 1

Lung Cancer Biomarkers

Column #1 Biomarker #	Column #2 Biomarker Designation	Column #3 Alternate Protein Names	Column #4 Gene Designation (Entrez Gene Link)	Column #5 Benign Nodule versus NSCLC	Column #6 Smokers versus NSCLC
1	AMPM2	Methionine aminopeptidase 2 p67eIF2 p67 Initiation factor 2-associated 67 kDa glycoprotein Peptidase M 2 MetAP 2 MAP 2	METAP2		X
2	Apo A-I	apolipoprotein A-I Apolipoprotein A-1	APOA1	X	
3	b-ECGF	FGF acidic FGF1 beta-ECGF Beta-endothelial cell growth factor	FGF1	X	
4	BLC	BLC B lymphocyte chemoattractant Small inducible cytokine B13 CXCL13 BCA-1	CXCL13	X	X
5	BMP-1	Bone morphogenetic protein 1 Procollagen C-proteinase PCP Mammalian tolloid protein mTId	BMP1	X	X
6	BTK	Tyrosine-protein kinase BTK Bruton tyrosine kinase Agammaglobulinaemia tyrosine kinase ATK B-cell progenitor kinase	BTK		X
7	C1s	Complement C1s subcomponent C1s, Activated, Two-Chain Form	C1S		X
8	C9	Complement component C9	C9	X	X
9	Cadherin E	Cadherin-1 Epithelial cadherin E-cadherin Uvomorulin CAM 120/80 CD_antigen = CD324	CDH1	X	
10	Cadherin-6	Kidney-cadherin K-cadherin	CDH6	X	
11	Calpain I	Calpain I (dimer of Calpain-1 catalytic subunit and Calpain small subunit 1) synonyms of the catalytic subunit include Calpain-1 large subunit: Calcium-activated neutral proteinase 1 Micromolar-calpain Cell proliferation-inducing gene 30 protein synonyms of the small subunit include: Calcium-dependent protease small	CAPN1 CAPNS1	X	

TABLE 1-continued

Lung Cancer Biomarkers

Column #1 Biomarker #	Column #2 Biomarker Designation	Column #3 Alternate Protein Names	Column #4 Gene Designation (Entrez Gene Link)	Column #5 Benign Nodule versus NSCLC	Column #6 Smokers versus NSCLC
		subunit 1 Calcium-activated neutral proteinase small subunit CANP small subunit			
12	Catalase	Catalase	CAT	X	
13	CATC	Dipeptidyl-peptidase 1 precursor Dipeptidyl-peptidase I DPP-I DPPI Cathepsin C Cathepsin J Dipeptidyl transferase	CTSC	X	
14	Cathepsin H	Cathepsin H	CTSH	X	
15	CD30 Ligand	Tumor necrosis factor ligand superfamily member 8 CD30-L CD153 antigen	TNFSF8	X	X
16	CDK5-p35	CDK5/p35 is a dimer of Cell division protein kinase 5, and the p35 chain of Cyclin-dependent kinase 5 activator 1 Cell division protein kinase 5 is also known as: Cyclin-dependent kinase 5 Tau protein kinase II catalytic subunit Serine/threonine-protein kinase PSSALRE p35 chain of Cyclin-dependent kinase 5 activator 1 is also known as: Cyclin-dependent kinase 5 regulatory subunit 1 CDK5 activator 1 Cyclin-dependent kinase 5 regulatory subunit 1 Tau protein kinase II regulatory subunit.	CDK5 CDK5R1		X
17	CK-MB	Creatine Phosphokinase-MB Isoenzyme, which is a dimer of Creatine kinase M-type and B-type Creatine kinase M and B chains M-CK and B-CK CKM and CKB	CKB CKM	X	X
18	CNDP1	Beta-Ala-His dipeptidase Carnosine dipeptidase 1 CNDP dipeptidase 1 Serum carnosinase Glutamate carboxypeptidase-like protein 2	CNDP1	X	X
19	Contactin-5	Neural recognition molecule NB-2 hNB-2	CNTN5		X
20	CSK	Tyrosine-protein kinase CSK C-SRC kinase Protein-tyrosine kinase CYL	CSK	X	X
21	Cyclophilin A	Cyclophilin A Peptidyl-prolyl cis-trans isomerase A PPIase Peptidylprolyl isomerase Cyclosporin A-binding protein Rotamase A PPIase A	PPIA		X
22	Endostatin	Endostatin, which is cleaved from Collagen alpha-1(XVIII) chain	COL18A1		X
23	ERBB1	Epidermal growth factor receptor Receptor tyrosine-protein kinase ErbB-1 EGFR HER1	EGFR	X	X

TABLE 1-continued

Lung Cancer Biomarkers

Column #1 Biomarker #	Column #2 Biomarker Designation	Column #3 Alternate Protein Names	Column #4 Gene Designation (Entrez Gene Link)	Column #5 Benign Nodule versus NSCLC	Column #6 Smokers versus NSCLC
24	FGF-17	Fibroblast Growth Factor-17	FGF17	X	X
25	FYN	Proto-oncogene tyrosine-protein kinase Fyn Protooncogene Syn p59-Fyn	FYN		X
26	GAPDH, liver	Glyceraldehyde 3-phosphate dehydrogenase	GAPDH	X	X
27	HMG-1	High mobility group protein B1 amphoterin Neurite growth-promoting protein	HMGB1	X	
28	HSP 90a	Heat shock protein HSP 90-alpha HSP 86 Renal carcinoma antigen NY-REN-38	HSP90AA1	X	X
29	HSP 90b	Heat shock protein HSP 90-beta HSP 90 HSP 84	HSP90AB1	X	
30	IGFBP-2	Insulin-like growth factor-binding protein 2 (IGF-binding protein 2; IGFBP-2; IBP-2; BP2)	IGFBP2	X	X
31	IL-15 Ra	Interleukin-15 receptor subunit alpha	IL15RA		X
32	IL-17B	Interleukin-17B Neuronal interleukin-17 related factor Interleukin-20 Cytokine-like protein ZCYTO7	IL17B	X	
33	IMB1	Importin subunit beta-1 Karyopherin subunit beta-1 Nuclear factor P97 Importin-90	KPNB1	X	
34	Kallikrein 7	Kallikrein-7 hK7 Stratum corneum chymotryptic enzyme hSCCE Serine protease 6	KLK7		X
35	KPCI	Protein kinase C iota type nPKC-iota Atypical protein kinase C-lambda/iota aPKC-lambda/iota PRKC-lambda/iota	PRKCI	X	X
36	LDH-H 1	L-lactate dehydrogenase B chain LDH-B LDH heart subunit LDH-H Renal carcinoma antigen NY-REN-46	LDHB		X
37	LGMN	Legumain Protease, cysteine 1 Asparaginyl endopeptidase	LGMN	X	
38	LRIG3	Leucine-rich repeats and immunoglobulin-like domains protein 3	LRIG3	X	X
39	Macrophage mannose receptor	Macrophage mannose receptor 1 MMR C-type lectin domain family 13 member D CD_antigen = CD206	MRC1	X	
40	MEK1	Dual specificity mitogen-activated protein kinase kinase 1 MAPK/ERK kinase 1 ERK activator kinase 1	MAP2K1	X	X
41	METAP1	Methionine aminopeptidase 1 MetAP 1 MAP 1 Peptidase M1	METAP1	X	
42	Midkine	Neurite outgrowth-promoting protein Neurite outgrowth-promoting factor 2 Midgestation and kidney protein Amphiregulin-associated protein ARAP	MDK		X

TABLE 1-continued

Lung Cancer Biomarkers

Column #1 Biomarker #	Column #2 Biomarker Designation	Column #3 Alternate Protein Names	Column #4 Gene Designation (Entrez Gene Link)	Column #5 Benign Nodule versus NSCLC	Column #6 Smokers versus NSCLC
43	MIP-5	C-C motif chemokine 15 Small-inducible cytokine A15 Macrophage inflammatory protein 5 Chemokine CC-2 HCC-2 NCC-3 MIP-1 delta Leukotactin-1 LKN-1 Mrp-2b	MIP5		X
44	MK13	Mitogen-activated protein kinase 13 MAP kinase p38 delta Mitogen-activated protein kinase p38 delta Stress-activated protein kinase 4	MAPK13	X	
45	MMP-7	Matrilysin Pump-1 protease Uterine metalloproteinase Matrix metalloproteinase-7 MMP-7 Matrin	MMP7	X	
46	NACA	Nascent polypeptide-associated complex subunit alpha NAC-alpha Alpha-NAC Allergen = Hom s 2	NACA	X	
47	NAGK	N-acetylglucosamine kinase GlcNAc kinase	NAGK	X	
48	PARC	C-C motif chemokine 18 Small-inducible cytokine A18 Macrophage inflammatory protein 4 MIP-4 Pulmonary and activation-regulated chemokine CC chemokine PARC Alternative macrophage activation-associated CC chemokine 1 AMAC-1 Dendritic cell chemokine 1 DC-CK1	CCL18		X
49	Proteinase-3	Proteinase-3 PR-3 AGP7 P29 Myeloblastin Leukocyte proteinase 3 Wegener's autoantigen Neutrophil proteinase 4 NP4 C-ANCA antigen	PRTN3	X	
50	Prothrombin	Prothrombin (Coagulation factor II)	F2	X	X
51	PTN	Pleiotrophin Heparin-binding growth-associated molecule HB-GAM Heparin-binding growth factor 8 HBGF-8 Osteoblast-specific factor 1 OSF-1 Heparin-binding neurite outgrowth-promoting factor 1 HBNF-1 Heparin-binding brain mitogen HBBM	PTN		X
52	RAC1	Ras-related C3 botulinum toxin substrate 1 p21-Rac1 Ras-like protein TC25 Cell migration-inducing gene 5 protein	RAC1		X
53	Renin	Renin Angiotensinogenase	REN		X

TABLE 1-continued

Lung Cancer Biomarkers

Column #1 Biomarker #	Column #2 Biomarker Designation	Column #3 Alternate Protein Names	Column #4 Gene Designation (Entrez Gene Link)	Column #5 Benign Nodule versus NSCLC	Column #6 Smokers versus NSCLC
54	RGM-C	Hemojuvelin Hemochromatosis type 2 protein RGM domain family member C	HFE2	X	
55	SCF sR	Mast/stem cell growth factor receptor (SCFR; Proto-oncogene tyrosine-protein kinase Kit; c-kit; CD_antigen = CD117)	KIT	X	X
56	sL-Selectin	sL-Selectin Leukocyte adhesion molecule-1 Lymph node homing receptor LAM-1 L-Selectin L-Selectin, soluble Leukocyte surface antigen Leu-8 TQ1 gp90-MEL Leukocyte-endothelial cell adhesion molecule 1 LECAM1 CD62 antigen-like family member L	SELL		X
57	TCTP	Translationally-controlled tumor protein p23 Histamine-releasing factor HRF Fortilin	TPT1		X
58	UBE2N	Ubiquitin-conjugating enzyme E2 N Ubiquitin-protein ligase N Ubiquitin carrier protein N Ubc13 Bendless-like ubiquitin-conjugating enzyme	UBE2N		X
59	Ubiquitin + 1	Ubiquitin	RPS27A		X
60	VEGF	Vascular endothelial growth factor A VEGF-A Vascular permeability factor	VEGFA	X	
61	YES	Proto-oncogene tyrosine-protein kinase Yes c-Yes p61-Yes	YES	X	

TABLE 2

100 Panels of 3 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers			Sensitivity	Specificity	Sens. + Spec.	AUC
1	ApoA-I	LRIG3	HSP90a	0.803	0.769	1.572	0.848
2	BLC	CK-MB	METAP1	0.779	0.795	1.575	0.839
3	BMP-1	ERBB1	METAP1	0.812	0.783	1.596	0.856
4	C9	ERBB1	KPCI	0.789	0.802	1.591	0.853
5	CATC	HSP90a	ERBB1	0.779	0.776	1.556	0.832
6	CD30Ligand	SCFsR	KPCI	0.784	0.793	1.577	0.839
7	CK-MB	CNDP1	HSP90a	0.779	0.795	1.575	0.851
8	CSK	CadherinE	ERBB1	0.831	0.776	1.607	0.881
9	Cadherin-6	CadherinE	ERBB1	0.756	0.812	1.568	0.851
10	CalpainI	ERBB1	CadherinE	0.808	0.805	1.612	0.88
11	Catalase	KPCI	ERBB1	0.779	0.783	1.563	0.849
12	CathepsinH	KPCI	CadherinE	0.756	0.802	1.558	0.845
13	FGF-17	HSP90b	ERBB1	0.775	0.812	1.587	0.852
14	CadherinE	GAPDH, liver	MMP-7	0.812	0.793	1.605	0.869
15	HMG-1	CK-MB	ERBB1	0.775	0.81	1.584	0.849
16	IGFBP-2	ERBB1	GAPDH, liver	0.793	0.81	1.603	0.854
17	IL-17B	CK-MB	METAP1	0.798	0.776	1.574	0.839
18	CadherinE	IMB1	ERBB1	0.808	0.788	1.596	0.867
19	LGMN	CadherinE	ERBB1	0.775	0.8	1.575	0.856
20	MEK1	CK-MB	ERBB1	0.751	0.829	1.58	0.83

TABLE 2-continued

21	CK-MB	MK13	HSP90a	0.779	0.81	1.589	0.854
22	MMR	KPCI	CadherinE	0.803	0.81	1.612	0.86
23	NACA	CadherinE	C9	0.789	0.79	1.579	0.835
24	MMP-7	NAGK	CadherinE	0.793	0.793	1.586	0.857
25	Proteinase-3	CadherinE	ERBB1	0.746	0.814	1.561	0.851
26	CK-MB	Prothrombin	HSP90a	0.803	0.762	1.565	0.857
27	RGM-C	HSP90b	ERBB1	0.784	0.819	1.603	0.854
28	VEGF	ERBB1	CadherinE	0.77	0.817	1.587	0.848
29	YES	HSP90a	ERBB1	0.817	0.776	1.593	0.872
30	b-ECGF	CK-MB	HSP90a	0.793	0.795	1.589	0.857
31	ApoA-I	KPCI	CadherinE	0.765	0.805	1.57	0.836
32	BLC	CadherinE	IMB1	0.803	0.769	1.572	0.847
33	CK-MB	BMP-1	METAP1	0.789	0.793	1.582	0.852
34	CATC	KPCI	ERBB1	0.789	0.76	1.548	0.831
35	CD30Ligand	CadherinE	ERBB1	0.77	0.8	1.57	0.846
36	CNDP1	ERBB1	METAP1	0.808	0.767	1.574	0.854
37	CK-MB	ERBB1	CSK	0.793	0.807	1.601	0.874
38	Cadherin-6	CK-MB	ERBB1	0.732	0.826	1.559	0.827
39	MMP-7	CalpainI	CadherinE	0.812	0.798	1.61	0.868
40	Catalase	CadherinE	ERBB1	0.775	0.779	1.553	0.854
41	CathepsinH	RGM-C	HSP90a	0.793	0.762	1.555	0.848
42	FGF-17	GAPDH, liver	ERBB1	0.779	0.798	1.577	0.858
43	HMG-1	MMP-7	CadherinE	0.784	0.798	1.582	0.858
44	RGM-C	IGFBP-2	HSP90a	0.803	0.774	1.577	0.853
45	IL-17B	CK-MB	GAPDH, liver	0.784	0.786	1.57	0.842
46	LGMN	MMP-7	CadherinE	0.779	0.788	1.567	0.845
47	CK-MB	LRIG3	HSP90a	0.817	0.795	1.612	0.866
48	YES	MEK1	ERBB1	0.732	0.838	1.57	0.839
49	MK13	METAP1	ERBB1	0.789	0.786	1.574	0.851
50	CadherinE	GAPDH, liver	MMR	0.808	0.786	1.593	0.867
51	NACA	METAP1	ERBB1	0.798	0.781	1.579	0.837
52	RGM-C	NAGK	ERBB1	0.779	0.8	1.579	0.856
53	Proteinase-3	GAPDH, liver	ERBB1	0.761	0.79	1.551	0.851
54	Prothrombin	CSK	ERBB1	0.812	0.752	1.565	0.847
55	CadherinE	SCFsR	KPCI	0.789	0.805	1.593	0.865
56	VEGF	CalpainI	CadherinE	0.808	0.776	1.584	0.849
57	b-ECGF	METAP1	ERBB1	0.812	0.776	1.588	0.852
58	ApoA-I	ERBB1	METAP1	0.793	0.776	1.57	0.856
59	BLC	CK-MB	CSK	0.756	0.812	1.568	0.832
60	CNDP1	BMP-1	METAP1	0.779	0.793	1.572	0.838
61	CadherinE	C9	KPCI	0.779	0.807	1.586	0.853
62	CATC	CalpainI	ERBB1	0.793	0.755	1.548	0.835
63	CD30Ligand	IMB1	ERBB1	0.789	0.779	1.567	0.848
64	Cadherin-6	HSP90a	ERBB1	0.746	0.805	1.551	0.839
65	YES	Catalase	ERBB1	0.784	0.769	1.553	0.848
66	CathepsinH	ERBB1	METAP1	0.765	0.788	1.553	0.849
67	FGF-17	CalpainI	ERBB1	0.789	0.788	1.577	0.859
68	HMG-1	CadherinE	ERBB1	0.793	0.788	1.582	0.867
69	CadherinE	HSP90b	ERBB1	0.817	0.812	1.629	0.872
70	CadherinE	IGFBP-2	KPCI	0.775	0.8	1.575	0.863
71	IL-17B	CK-MB	HSP90a	0.789	0.779	1.567	0.839
72	LGMN	CalpainI	ERBB1	0.761	0.802	1.563	0.838
73	CK-MB	LRIG3	HSP90b	0.779	0.814	1.594	0.836
74	MEK1	CadherinE	ERBB1	0.765	0.802	1.568	0.857
75	CadherinE	MK13	ERBB1	0.761	0.81	1.57	0.853
76	MMR	HSP90b	CadherinE	0.793	0.786	1.579	0.852
77	NACA	HSP90a	ERBB1	0.789	0.788	1.577	0.846
78	CadherinE	NAGK	ERBB1	0.789	0.79	1.579	0.871
79	Proteinase-3	IMB1	ERBB1	0.77	0.776	1.546	0.838
80	Prothrombin	METAP1	ERBB1	0.793	0.767	1.56	0.842
81	SCFsR	ERBB1	KPCI	0.784	0.805	1.589	0.854
82	VEGF	HSP90b	CadherinE	0.793	0.788	1.582	0.84
83	b-ECGF	CadherinE	CalpainI	0.779	0.793	1.572	0.848
84	ApoA-I	CSK	ERBB1	0.775	0.783	1.558	0.861
85	BLC	CadherinE	KPCI	0.779	0.783	1.563	0.852
86	BMP-1	CadherinE	KPCI	0.784	0.783	1.567	0.849
87	C9	ERBB1	CadherinE	0.756	0.829	1.584	0.845
88	CATC	GAPDH, liver	ERBB1	0.779	0.767	1.546	0.843
89	CD30Ligand	METAP1	ERBB1	0.793	0.769	1.562	0.851
90	CNDP1	CadherinE	KPCI	0.77	0.8	1.57	0.856
91	Cadherin-6	HSP90b	ERBB1	0.756	0.795	1.551	0.834
92	Catalase	MK13	ERBB1	0.77	0.774	1.544	0.838
93	CathepsinH	METAP1	CadherinE	0.784	0.769	1.553	0.851
94	FGF-17	METAP1	ERBB1	0.793	0.783	1.577	0.855
95	HMG-1	METAP1	ERBB1	0.784	0.776	1.56	0.839
96	IGFBP-2	ERBB1	METAP1	0.789	0.786	1.574	0.858
97	IL-17B	CadherinE	HSP90b	0.761	0.805	1.565	0.84
98	LGMN	METAP1	ERBB1	0.779	0.779	1.558	0.834
99	LRIG3	CadherinE	HSP90b	0.798	0.788	1.586	0.852
100	MEK1	HSP90b	ERBB1	0.761	0.795	1.556	0.841

TABLE 2-continued

Marker	Count	Marker	Count
ERBB1	59	FGF-17	4
CadherinE	39	CathepsinH	4
METAP1	18	Catalase	4
CK-MB	16	Cadherin-6	4
KPCI	14	CNDP1	4
HSP90a	13	CD30Ligand	4
HSP90b	10	CATC	4
GAPDH, liver	7	C9	4
CalpainI	7	BMP-1	4
MMP-7	5	BLC	4
CSK	5	ApoA-I	4
RGM-C	4	b-ECGF	3
MK13	4	YES	3
MEK1	4	VEGF	3
LRIG3	4	SCFsR	3
LGMN	4	Prothrombin	3
IMB1	4	Proteinase-3	3
IL-17B	4	NAGK	3
IGFBP-2	4	NACA	3
HMG-1	4	MMR	3

TABLE 3

100 Panels of 4 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers				Sensitivity	Specificity	Sens. + Spec.	AUC
1	ApoA-I	KPCI	CadherinE	MMR	0.836	0.79	1.626	0.865
2	BLC	ERBB1	CSK	CK-MB	0.808	0.821	1.629	0.859
3	CK-MB	BMP-1	METAP1	ERBB1	0.831	0.802	1.633	0.874
4	C9	ERBB1	CadherinE	KPCI	0.836	0.802	1.638	0.873
5	CATC	CadherinE	HSP90b	ERBB1	0.822	0.788	1.61	0.861
6	CD30Ligand	KPCI	CK-MB	ERBB1	0.822	0.819	1.641	0.86
7	CK-MB	CNDP1	CSK	ERBB1	0.817	0.817	1.634	0.869
8	Cadherin-6	KPCI	ERBB1	CadherinE	0.812	0.8	1.612	0.863
9	RGM-C	CadherinE	CalpainI	ERBB1	0.845	0.8	1.645	0.892
10	Catalase	METAP1	ERBB1	CK-MB	0.836	0.783	1.619	0.874
11	CathepsinH	SCFsR	CadherinE	KPCI	0.822	0.8	1.622	0.87
12	CK-MB	FGF-17	ERBB1	METAP1	0.85	0.793	1.643	0.874
13	CadherinE	IGFBP-2	GAPDH, liver	CK-MB	0.831	0.807	1.638	0.886
14	HMG-1	C9	ERBB1	CadherinE	0.812	0.812	1.624	0.869
15	YES	CK-MB	ERBB1	HSP90a	0.831	0.821	1.652	0.884
16	IL-17B	METAP1	ERBB1	CK-MB	0.84	0.795	1.636	0.87
17	IGFBP-2	MMP-7	CadherinE	IMB1	0.854	0.776	1.631	0.875
18	LGMN	KPCI	ERBB1	CadherinE	0.822	0.798	1.619	0.865
19	CK-MB	HSP90b	CadherinE	LRIG3	0.826	0.814	1.641	0.873
20	MEK1	METAP1	ERBB1	CK-MB	0.822	0.805	1.626	0.87
21	MK13	HSP90b	ERBB1	CadherinE	0.822	0.814	1.636	0.875
22	NACA	LRIG3	HSP90a	CK-MB	0.831	0.795	1.626	0.846
23	CK-MB	ERBB1	CadherinE	NAGK	0.798	0.821	1.62	0.886
24	Proteinase-3	KPCI	ERBB1	CadherinE	0.798	0.817	1.615	0.869
25	Prothrombin	CadherinE	MMP-7	CalpainI	0.85	0.776	1.626	0.868
26	VEGF	CSK	ERBB1	CadherinE	0.84	0.8	1.64	0.883
27	CadherinE	GAPDH, liver	MMR	b-ECGF	0.831	0.79	1.621	0.865
28	ApoA-I	ERBB1	METAP1	CadherinE	0.845	0.779	1.624	0.882
29	BLC	SCFsR	KPCI	CadherinE	0.831	0.79	1.621	0.867
30	BMP-1	CadherinE	ERBB1	METAP1	0.85	0.776	1.626	0.878
31	CATC	CK-MB	KPCI	ERBB1	0.831	0.774	1.605	0.842
32	CD30Ligand	METAP1	CK-MB	ERBB1	0.826	0.798	1.624	0.871
33	CNDP1	SCFsR	CadherinE	KPCI	0.836	0.795	1.631	0.878
34	Cadherin-6	RGM-C	ERBB1	CadherinE	0.798	0.812	1.61	0.86
35	CK-MB	Catalase	KPCI	ERBB1	0.812	0.805	1.617	0.863
36	CathepsinH	ERBB1	CadherinE	METAP1	0.84	0.781	1.621	0.876
37	CK-MB	FGF-17	ERBB1	GAPDH, liver	0.808	0.826	1.634	0.868
38	HMG-1	KPCI	MMP-7	CadherinE	0.822	0.802	1.624	0.865
39	IL-17B	CadherinE	ERBB1	HSP90b	0.826	0.805	1.631	0.874
40	RGM-C	CadherinE	ERBB1	IMB1	0.831	0.798	1.629	0.879
41	YES	CadherinE	ERBB1	LGMN	0.798	0.814	1.612	0.868
42	MEK1	CadherinE	HSP90b	ERBB1	0.812	0.812	1.624	0.877
43	CadherinE	MK13	MMR	KPCI	0.826	0.8	1.626	0.871
44	NACA	CadherinE	MMR	ERBB1	0.84	0.781	1.621	0.87
45	RGM-C	CadherinE	MMR	NAGK	0.812	0.807	1.619	0.867
46	Proteinase-3	KPCI	CK-MB	CadherinE	0.789	0.824	1.613	0.861
47	Prothrombin	HSP90b	ERBB1	RGM-C	0.798	0.826	1.624	0.856

TABLE 3-continued

48	VEGF	ERBB1	HSP90a	CadherinE	0.817	0.817	1.634	0.877
49	b-ECGF	CadherinE	ERBB1	HSP90b	0.812	0.807	1.619	0.876
50	ApoA-I	MMP-7	CadherinE	KPCI	0.831	0.79	1.621	0.869
51	BLC	ERBB1	METAP1	CK-MB	0.826	0.793	1.619	0.864
52	CK-MB	BMP-1	KPCI	CadherinE	0.808	0.814	1.622	0.869
53	C9	ERBB1	METAP1	CadherinE	0.845	0.781	1.626	0.884
54	CD30Ligand	KPCI	CadherinE	ERBB1	0.822	0.8	1.622	0.875
55	CNDP1	ERBB1	CadherinE	IMB1	0.831	0.795	1.626	0.878
56	Cadherin-6	CadherinE	HSP90a	ERBB1	0.803	0.807	1.61	0.864
57	RGM-C	CK-MB	ERBB1	CalpainI	0.808	0.829	1.636	0.88
58	Catalase	HSP90b	ERBB1	CadherinE	0.826	0.788	1.614	0.87
59	CathepsinH	CSK	ERBB1	CadherinE	0.822	0.795	1.617	0.878
60	FGF-17	CadherinE	ERBB1	HSP90a	0.831	0.798	1.629	0.878
61	MMP-7	ERBB1	HMG-1	CadherinE	0.803	0.81	1.612	0.874
62	IGFBP-2	MMP-7	CadherinE	KPCI	0.869	0.779	1.647	0.874
63	IL-17B	SCFsR	KPCI	CadherinE	0.826	0.802	1.629	0.868
64	LGMN	METAP1	ERBB1	CadherinE	0.831	0.774	1.605	0.865
65	LRIG3	CadherinE	ERBB1	HSP90b	0.822	0.81	1.631	0.877
66	MEK1	MMP-7	CadherinE	GAPDH, liver	0.826	0.788	1.614	0.874
67	MK13	KPCI	ERBB1	CadherinE	0.822	0.802	1.624	0.869
68	NACA	CSK	C9	CadherinE	0.831	0.788	1.619	0.857
69	CK-MB	MMP-7	CadherinE	NAGK	0.798	0.819	1.617	0.873
70	Proteinase-3	CK-MB	ERBB1	GAPDH, liver	0.793	0.814	1.608	0.866
71	Prothrombin	CadherinE	ERBB1	IMB1	0.831	0.786	1.617	0.866
72	VEGF	KPCI	CadherinE	SCFsR	0.826	0.8	1.626	0.868
73	YES	RGM-C	HSP90a	ERBB1	0.836	0.807	1.643	0.887
74	b-ECGF	CK-MB	METAP1	ERBB1	0.822	0.798	1.619	0.875
75	ApoA-I	RGM-C	HSP90a	IGFBP-2	0.84	0.776	1.617	0.862
76	BLC	ERBB1	METAP1	RGM-C	0.831	0.786	1.617	0.866
77	METAP1	HSP90b	BMP-1	CadherinE	0.817	0.802	1.619	0.862
78	CD30Ligand	METAP1	ERBB1	YES	0.836	0.786	1.621	0.857
79	CNDP1	IMB1	CadherinE	IGFBP-2	0.831	0.793	1.624	0.872
80	Cadherin-6	C9	CadherinE	ERBB1	0.784	0.817	1.601	0.855
81	CK-MB	ERBB1	CadherinE	CalpainI	0.817	0.817	1.634	0.894
82	Catalase	CadherinE	ERBB1	IMB1	0.84	0.774	1.614	0.866
83	CathepsinH	ERBB1	HSP90b	CadherinE	0.803	0.807	1.61	0.866
84	FGF-17	CadherinE	ERBB1	CalpainI	0.817	0.807	1.624	0.881
85	HMG-1	MMR	ERBB1	CadherinE	0.808	0.805	1.612	0.878
86	IL-17B	CK-MB	KPCI	ERBB1	0.817	0.805	1.622	0.856
87	LGMN	CadherinE	ERBB1	C9	0.789	0.814	1.603	0.857
88	LRIG3	CadherinE	HSP90a	CK-MB	0.812	0.814	1.626	0.882
89	MEK1	METAP1	ERBB1	CadherinE	0.822	0.788	1.61	0.875
90	CadherinE	MK13	KPCI	CK-MB	0.798	0.824	1.622	0.862
91	NACA	CadherinE	HSP90a	ERBB1	0.826	0.79	1.617	0.868
92	MMP-7	NAGK	CadherinE	KPCI	0.817	0.8	1.617	0.862
93	Proteinase-3	KPCI	ERBB1	CK-MB	0.798	0.807	1.605	0.855
94	RGM-C	Prothrombin	HSP90a	CK-MB	0.836	0.781	1.617	0.875
95	VEGF	METAP1	CadherinE	ERBB1	0.845	0.779	1.624	0.88
96	b-ECGF	KPCI	CadherinE	C9	0.812	0.805	1.617	0.851
97	ApoA-I	BMP-1	KPCI	CadherinE	0.817	0.795	1.612	0.857
98	BLC	IGFBP-2	KPCI	CadherinE	0.817	0.795	1.612	0.865
99	CD30Ligand	GAPDH, liver	ERBB1	CadherinE	0.817	0.802	1.619	0.879
100	CNDP1	ERBB1	CadherinE	KPCI	0.817	0.8	1.617	0.875

Marker	Count	Marker	Count
CadherinE	74	BLC	5
ERBB1	68	ApoA-I	5
CK-MB	30	b-ECGF	4
KPCI	29	YES	4
METAP1	18	VEGF	4
HSP90b	11	Prothrombin	4
RGM-C	10	Proteinase-3	4
HSP90a	10	NAGK	4
MMP-7	9	NACA	4
C9	7	MK13	4
MMR	6	MEK1	4
IMB1	6	LRIG3	4
IGFBP-2	6	LGMN	4
GAPDH, liver	6	IL-17B	4
SCFsR	5	HMG-1	4
CalpainI	5	FGF-17	4
CSK	5	CathepsinH	4
CNDP1	5	Catalase	4
CD30Ligand	5	Cadherin-6	4
BMP-1	5	CATC	2

TABLE 4

100 Panels of 5 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers					Sensitivity	Specificity	Sens. + Spec.	AUC
1	ApoA-I	ERBB1	METAP1	RGM-C	CadherinE	0.873	0.79	1.664	0.89
2	BLC	CadherinE	HSP90a	ERBB1	RGM-C	0.822	0.831	1.653	0.877
3	CK-MB	HSP90b	ERBB1	CSK	BMP-1	0.84	0.814	1.655	0.873
4	CSK	CadherinE	CK-MB	C9	KPCI	0.85	0.805	1.655	0.877
5	RGM-C	CadherinE	CalpainI	ERBB1	CATC	0.854	0.786	1.64	0.877
6	CD30Ligand	RGM-C	ERBB1	CalpainI	CadherinE	0.859	0.807	1.666	0.891
7	CSK	IMB1	MMP-7	CadherinE	CNDP1	0.878	0.793	1.671	0.879
8	Cadherin-6	KPCI	ERBB1	CadherinE	SCFsR	0.85	0.79	1.64	0.875
9	CadherinE	IGFBP-2	GAPDH, liver	Catalase	CK-MB	0.864	0.802	1.666	0.886
10	CathepsinH	ERBB1	CadherinE	METAP1	CK-MB	0.864	0.795	1.659	0.892
11	CK-MB	FGF-17	ERBB1	HSP90a	YES	0.822	0.831	1.653	0.884
12	HMG-1	CK-MB	CadherinE	ERBB1	YES	0.836	0.829	1.664	0.893
13	CadherinE	SCFsR	GAPDH, liver	CK-MB	IL-17B	0.836	0.829	1.664	0.885
14	RGM-C	CadherinE	ERBB1	HSP90a	LGMN	0.836	0.814	1.65	0.879
15	CSK	HSP90b	CadherinE	LRIG3	CK-MB	0.859	0.817	1.676	0.88
16	MEK1	RGM-C	ERBB1	CadherinE	HSP90b	0.84	0.829	1.669	0.887
17	YES	CK-MB	HSP90a	MK13	ERBB1	0.831	0.829	1.66	0.878
18	MMR	METAP1	CadherinE	RGM-C	ERBB1	0.873	0.795	1.668	0.901
19	NACA	CadherinE	CK-MB	HSP90a	ERBB1	0.85	0.807	1.657	0.879
20	CK-MB	ERBB1	CadherinE	RGM-C	NAGK	0.836	0.829	1.664	0.896
21	Proteinase-3	SCFsR	KPCI	CK-MB	CadherinE	0.836	0.821	1.657	0.878
22	Prothrombin	CadherinE	CK-MB	CalpainI	ERBB1	0.854	0.812	1.666	0.895
23	VEGF	HSP90b	ERBB1	CadherinE	RGM-C	0.854	0.817	1.671	0.886
24	b-ECGF	CK-MB	CadherinE	GAPDH, liver	IGFBP-2	0.836	0.819	1.655	0.887
25	ApoA-I	KPCI	ERBB1	CadherinE	MMP-7	0.845	0.812	1.657	0.881
26	RGM-C	BLC	HSP90a	ERBB1	YES	0.822	0.831	1.653	0.871
27	BMP-1	CadherinE	IMB1	RGM-C	ERBB1	0.854	0.8	1.654	0.881
28	CSK	SCFsR	CadherinE	C9	KPCI	0.854	0.8	1.654	0.879
29	CATC	METAP1	ERBB1	CK-MB	YES	0.84	0.793	1.633	0.858
30	CD30Ligand	HSP90b	CadherinE	ERBB1	RGM-C	0.84	0.821	1.662	0.884
31	CNDP1	LRIG3	KPCI	SCFsR	CadherinE	0.85	0.812	1.662	0.879
32	Cadherin-6	CK-MB	CadherinE	ERBB1	KPCI	0.822	0.817	1.638	0.878
33	Catalase	METAP1	MMP-7	CadherinE	CK-MB	0.878	0.776	1.654	0.886
34	CathepsinH	ERBB1	CadherinE	METAP1	RGM-C	0.873	0.781	1.654	0.89
35	CK-MB	FGF-17	ERBB1	HSP90b	CadherinE	0.826	0.824	1.65	0.886
36	MMR	KPCI	CadherinE	HMG-1	SCFsR	0.845	0.805	1.65	0.876
37	IL-17B	GAPDH, liver	ERBB1	CK-MB	CadherinE	0.84	0.824	1.664	0.889
38	CK-MB	ERBB1	CadherinE	HSP90a	LGMN	0.817	0.829	1.645	0.887
39	ERBB1	HSP90a	CadherinE	MEK1	RGM-C	0.845	0.814	1.659	0.885
40	CadherinE	MK13	KPCI	CK-MB	ERBB1	0.826	0.831	1.657	0.883
41	NACA	CadherinE	ERBB1	CSK	MMR	0.873	0.781	1.654	0.884
42	YES	NAGK	CadherinE	ERBB1	CK-MB	0.84	0.821	1.662	0.895
43	Proteinase-3	KPCI	ERBB1	CadherinE	CNDP1	0.84	0.805	1.645	0.876
44	Prothrombin	CalpainI	ERBB1	RGM-C	CadherinE	0.859	0.8	1.659	0.889
45	VEGF	CalpainI	ERBB1	METAP1	CadherinE	0.878	0.786	1.664	0.88
46	b-ECGF	CK-MB	CadherinE	GAPDH, liver	MMP-7	0.854	0.8	1.654	0.883
47	CalpainI	ERBB1	CadherinE	ApoA-I	RGM-C	0.854	0.8	1.654	0.895
48	BLC	ERBB1	METAP1	YES	CK-MB	0.836	0.814	1.65	0.867
49	CNDP1	BMP-1	IMB1	CadherinE	ERBB1	0.845	0.807	1.652	0.879
50	SCFsR	C9	METAP1	KPCI	CadherinE	0.854	0.798	1.652	0.874
51	CK-MB	SCFsR	KPCI	CadherinE	CATC	0.85	0.781	1.631	0.865
52	CD30Ligand	KPCI	CK-MB	CadherinE	SCFsR	0.845	0.817	1.662	0.882
53	Cadherin-6	CadherinE	HSP90a	ERBB1	RGM-C	0.826	0.807	1.633	0.874
54	Catalase	HSP90b	ERBB1	CadherinE	CK-MB	0.85	0.802	1.652	0.883
55	CathepsinH	CSK	ERBB1	CadherinE	CK-MB	0.836	0.817	1.652	0.894
56	CK-MB	CNDP1	METAP1	ERBB1	FGF-17	0.85	0.8	1.65	0.873
57	CK-MB	MMP-7	CadherinE	HMG-1	ERBB1	0.808	0.84	1.648	0.886
58	IGFBP-2	ERBB1	CalpainI	RGM-C	CadherinE	0.845	0.826	1.671	0.901
59	IL-17B	CadherinE	ERBB1	HSP90b	RGM-C	0.84	0.824	1.664	0.881
60	LGMN	HSP90b	CadherinE	ERBB1	RGM-C	0.831	0.81	1.641	0.876
61	LRIG3	CadherinE	METAP1	HSP90b	MMP-7	0.878	0.786	1.664	0.874
62	MEK1	CalpainI	ERBB1	RGM-C	CadherinE	0.831	0.821	1.652	0.893
63	MK13	SCFsR	KPCI	CadherinE	MMR	0.854	0.802	1.657	0.883
64	NACA	CK-MB	ERBB1	CSK	CadherinE	0.85	0.8	1.65	0.885
65	CalpainI	ERBB1	CadherinE	NAGK	RGM-C	0.854	0.798	1.652	0.891
66	Proteinase-3	SCFsR	CadherinE	KPCI	CNDP1	0.836	0.807	1.643	0.877
67	CK-MB	MMP-7	CadherinE	Prothrombin	METAP1	0.883	0.776	1.659	0.887
68	RGM-C	CadherinE	CalpainI	VEGF	ERBB1	0.869	0.793	1.661	0.897
69	SCFsR	MMP-7	METAP1	b-ECGF	CadherinE	0.883	0.769	1.652	0.885
70	RGM-C	CadherinE	MMR	GAPDH, liver	ApoA-I	0.85	0.802	1.652	0.887
71	BLC	SCFsR	KPCI	CadherinE	MMP-7	0.85	0.798	1.647	0.875
72	BMP-1	CSK	CadherinE	HSP90b	RGM-C	0.85	0.802	1.652	0.873
73	BMP-1	CadherinE	KPCI	C9	METAP1	0.859	0.793	1.652	0.863
74	CATC	CadherinE	HSP90a	ERBB1	RGM-C	0.831	0.793	1.624	0.866
75	CD30Ligand	KPCI	CK-MB	CadherinE	ERBB1	0.84	0.817	1.657	0.887

TABLE 4-continued

76	Cadherin-6	RGM-C	ERBB1	CadherinE	CalpainI	0.836	0.798	1.633	0.876
77	CK-MB	Catalase	KPCI	CadherinE	IGFBP-2	0.854	0.798	1.652	0.879
78	CathepsinH	IMB1	CadherinE	ERBB1	RGM-C	0.859	0.79	1.65	0.882
79	CK-MB	ERBB1	CadherinE	NAGK	FGF-17	0.826	0.821	1.648	0.888
80	HMG-1	HSP90a	ERBB1	RGM-C	CadherinE	0.836	0.812	1.648	0.886
81	YES	CK-MB	ERBB1	METAP1	IL-17B	0.845	0.814	1.659	0.871
82	LGMN	CadherinE	ERBB1	C9	CSK	0.84	0.8	1.64	0.875
83	LRIG3	KPCI	CadherinE	SCFsR	CK-MB	0.85	0.812	1.662	0.879
84	YES	CK-MB	ERBB1	METAP1	MEK1	0.831	0.817	1.648	0.873
85	MK13	HSP90b	MMP-7	CadherinE	METAP1	0.859	0.793	1.652	0.871
86	NACA	CSK	MMP-7	CadherinE	ERBB1	0.873	0.776	1.649	0.883
87	Proteinase-3	KPCI	ERBB1	CK-MB	CadherinE	0.822	0.819	1.641	0.883
88	Prothrombin	CadherinE	ERBB1	KPCI	YES	0.845	0.807	1.652	0.872
89	VEGF	CadherinE	HSP90a	RGM-C	ERBB1	0.84	0.817	1.657	0.89
90	b-ECGF	CalpainI	ERBB1	CK-MB	CadherinE	0.822	0.829	1.65	0.894
91	ApoA-I	ERBB1	METAP1	RGM-C	CalpainI	0.85	0.8	1.65	0.865
92	BLC	CadherinE	CalpainI	ERBB1	RGM-C	0.836	0.81	1.645	0.884
93	RGM-C	CadherinE	ERBB1	HSP90a	CATC	0.831	0.793	1.624	0.866
94	CD30Ligand	CSK	ERBB1	CK-MB	YES	0.817	0.836	1.653	0.876
95	Cadherin-6	HSP90b	CadherinE	ERBB1	RGM-C	0.826	0.8	1.626	0.877
96	MMR	KPCI	CadherinE	Catalase	SCFsR	0.859	0.788	1.647	0.871
97	LRIG3	CadherinE	METAP1	HSP90b	CathepsinH	0.854	0.79	1.645	0.866
98	CK-MB	ERBB1	CadherinE	GAPDH, liver	FGF-17	0.826	0.821	1.648	0.888
99	HMG-1	KPCI	ERBB1	CadherinE	MMR	0.845	0.802	1.647	0.882
100	CK-MB	IGFBP-2	CSK	ERBB1	CadherinE	0.826	0.833	1.66	0.906

Marker	Count	Marker	Count
CadherinE	89	CathepsinH	5
ERBB1	71	Catalase	5
CK-MB	43	Cadherin-6	5
RGM-C	34	CD30Ligand	5
KPCI	24	CATC	5
METAP1	19	C9	5
SCFsR	15	BMP-1	5
HSP90b	14	BLC	5
CalpainI	14	ApoA-I	5
HSP90a	13	b-ECGF	4
CSK	13	VEGF	4
YES	11	Prothrombin	4
MMP-7	11	Proteinase-3	4
MMR	7	NAGK	4
GAPDH, liver	7	NACA	4
CNDP1	6	MK13	4
LRIG3	5	MEK1	4
IGFBP-2	5	LGMN	4
HMG-1	5	IMB1	4
FGF-17	5	IL-17B	4

TABLE 5

100 Panels of 6 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers						Sensitivity	Specificity	Sens. + Spec.	AUC
1	ApoA-I	ERBB1	METAP1	RGM-C	CalpainI	CadherinE	0.873	0.802	1.676	0.888
2	BLC	CadherinE	METAP1	ERBB1	CK-MB	YES	0.869	0.805	1.673	0.889
3	RGM-C	BMP-1	HSP90b	CadherinE	METAP1	MMR	0.869	0.802	1.671	0.881
4	RGM-C	C9	ERBB1	CadherinE	METAP1	CK-MB	0.878	0.8	1.678	0.905
5	RGM-C	CadherinE	CalpainI	ERBB1	CATC	CK-MB	0.864	0.79	1.654	0.889
6	RGM-C	CadherinE	KPCI	CK-MB	SCFsR	CD30Ligand	0.859	0.819	1.678	0.888
7	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.864	0.819	1.683	0.904
8	Cadherin-6	RGM-C	ERBB1	CadherinE	CalpainI	VEGF	0.845	0.814	1.659	0.88
9	CK-MB	IGFBP-2	KPCI	ERBB1	CadherinE	Catalase	0.869	0.805	1.673	0.892
10	CathepsinH	CadherinE	HSP90a	ERBB1	RGM-C	IGFBP-2	0.836	0.836	1.671	0.889
11	RGM-C	FGF-17	ERBB1	CalpainI	CadherinE	HSP90a	0.873	0.802	1.676	0.889
12	YES	CadherinE	ERBB1	RGM-C	GAPDH, liver	CK-MB	0.859	0.829	1.688	0.9
13	HMG-1	CK-MB	CadherinE	ERBB1	HSP90a	YES	0.864	0.821	1.685	0.897
14	METAP1	HSP90b	CadherinE	ERBB1	RGM-C	IL-17B	0.878	0.81	1.687	0.882
15	MMR	ERBB1	CadherinE	IMB1	CalpainI	RGM-C	0.873	0.805	1.678	0.894
16	CK-MB	ERBB1	CadherinE	HSP90a	LGMN	YES	0.859	0.821	1.681	0.891
17	CK-MB	CNDP1	KPCI	CadherinE	SCFsR	LRIG3	0.864	0.817	1.681	0.886
18	MEK1	CalpainI	ERBB1	RGM-C	CadherinE	CD30Ligand	0.869	0.807	1.676	0.889
19	MK13	MMP-7	KPCI	CadherinE	SCFsR	CK-MB	0.869	0.812	1.68	0.889
20	NACA	CadherinE	ERBB1	METAP1	CK-MB	MMP-7	0.878	0.795	1.673	0.889
21	YES	NAGK	CadherinE	ERBB1	CK-MB	HSP90a	0.878	0.814	1.692	0.897
22	Proteinase-3	KPCI	ERBB1	CK-MB	CadherinE	CNDP1	0.859	0.821	1.681	0.885
23	CK-MB	CNDP1	KPCI	CadherinE	SCFsR	Prothrombin	0.873	0.81	1.683	0.885

TABLE 5-continued

24	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	CK-MB	0.845	0.829	1.674	0.895
25	ApoA-I	CSK	ERBB1	CK-MB	CadherinE	RGM-C	0.85	0.824	1.674	0.907
26	RGM-C	CadherinE	ERBB1	CSK	BLC	CK-MB	0.84	0.826	1.667	0.895
27	BMP-1	CadherinE	IMB1	CK-MB	ERBB1	LRIG3	0.859	0.81	1.669	0.883
28	SCFsR	C9	CadherinE	GAPDH, liver	KPCI	MMP-7	0.869	0.807	1.676	0.884
29	RGM-C	CadherinE	CalpainI	CK-MB	ERBB1	CATC	0.864	0.79	1.654	0.889
30	RGM-C	HSP90b	ERBB1	SCFsR	CadherinE	Cadherin-6	0.859	0.8	1.659	0.885
31	RGM-C	CadherinE	ERBB1	GAPDH, liver	CK-MB	Catalase	0.85	0.821	1.671	0.901
32	CathepsinH	RGM-C	METAP1	CK-MB	CadherinE	ERBB1	0.873	0.798	1.671	0.903
33	RGM-C	FGF-17	ERBB1	CalpainI	CadherinE	IGFBP-2	0.845	0.826	1.671	0.893
34	HMG-1	RGM-C	ERBB1	CadherinE	MMP-7	CK-MB	0.85	0.833	1.683	0.896
35	IL-17B	CalpainI	ERBB1	RGM-C	CadherinE	CK-MB	0.864	0.817	1.681	0.898
36	LGMN	HSP90b	CadherinE	ERBB1	RGM-C	SCFsR	0.869	0.81	1.678	0.886
37	MEK1	GAPDH, liver	ERBB1	CK-MB	CadherinE	YES	0.845	0.829	1.674	0.902
38	MK13	HSP90b	ERBB1	RGM-C	CadherinE	CK-MB	0.85	0.824	1.674	0.892
39	NACA	CadherinE	ERBB1	CSK	RGM-C	MMR	0.892	0.781	1.673	0.895
40	YES	CadherinE	ERBB1	RGM-C	NAGK	METAP1	0.897	0.788	1.685	0.885
41	Proteinase-3	KPCI	CK-MB	CadherinE	IGFBP-2	SCFsR	0.864	0.807	1.671	0.888
42	Prothrombin	CalpainI	ERBB1	RGM-C	CadherinE	CK-MB	0.864	0.812	1.676	0.904
43	VEGF	HSP90b	ERBB1	CadherinE	RGM-C	YES	0.873	0.814	1.688	0.888
44	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	METAP1	0.873	0.8	1.673	0.884
45	LRIG3	KPCI	CadherinE	SCFsR	ApoA-I	CNDP1	0.869	0.805	1.673	0.88
46	CadherinE	MK13	KPCI	CK-MB	ERBB1	BLC	0.845	0.819	1.664	0.879
47	BMP-1	CadherinE	ERBB1	KPCI	YES	SCFsR	0.864	0.805	1.669	0.888
48	CSK	CadherinE	C9	ERBB1	CD30Ligand	YES	0.859	0.812	1.671	0.883
49	RGM-C	CadherinE	CalpainI	ERBB1	CATC	IGFBP-2	0.85	0.802	1.652	0.881
50	LRIG3	KPCI	CadherinE	SCFsR	CK-MB	Cadherin-6	0.85	0.807	1.657	0.874
51	Catalase	CadherinE	ERBB1	KPCI	RGM-C	CK-MB	0.85	0.819	1.669	0.89
52	CSK	GAPDH, liver	ERBB1	CadherinE	YES	CathepsinH	0.873	0.798	1.671	0.89
53	RGM-C	FGF-17	ERBB1	CalpainI	CadherinE	CD30Ligand	0.859	0.812	1.671	0.884
54	HMG-1	RGM-C	ERBB1	CadherinE	MMR	CalpainI	0.859	0.819	1.678	0.901
55	IL-17B	CadherinE	ERBB1	METAP1	RGM-C	VEGF	0.883	0.795	1.678	0.884
56	CSK	IMB1	MMP-7	CadherinE	ERBB1	CK-MB	0.869	0.807	1.676	0.897
57	MMP-7	ERBB1	CadherinE	LGMN	CSK	YES	0.864	0.81	1.673	0.884
58	CalpainI	ERBB1	CadherinE	NAGK	RGM-C	MEK1	0.854	0.819	1.674	0.892
59	CK-MB	MMP-7	CadherinE	NACA	METAP1	RGM-C	0.887	0.783	1.671	0.884
60	Proteinase-3	CadherinE	ERBB1	RGM-C	CalpainI	MMP-7	0.859	0.81	1.669	0.893
61	Prothrombin	CadherinE	ERBB1	HSP90b	METAP1	YES	0.873	0.802	1.676	0.87
62	b-ECGF	CadherinE	ERBB1	METAP1	RGM-C	VEGF	0.873	0.8	1.673	0.886
63	ApoA-I	HSP90b	CadherinE	ERBB1	RGM-C	MEK1	0.845	0.826	1.671	0.89
64	BLC	ERBB1	METAP1	RGM-C	CK-MB	YES	0.859	0.805	1.664	0.881
65	RGM-C	BMP-1	ERBB1	METAP1	CadherinE	HSP90b	0.869	0.8	1.669	0.888
66	CK-MB	MMP-7	CadherinE	HMG-1	KPCI	C9	0.854	0.814	1.669	0.88
67	CK-MB	ERBB1	CadherinE	RGM-C	HSP90a	CATC	0.84	0.81	1.65	0.882
68	Cadherin-6	RGM-C	ERBB1	CadherinE	CalpainI	MMR	0.836	0.814	1.65	0.885
69	CadherinE	IGFBP-2	METAP1	ERBB1	CK-MB	Catalase	0.873	0.795	1.668	0.901
70	CathepsinH	ERBB1	CadherinE	METAP1	RGM-C	NAGK	0.869	0.798	1.666	0.889
71	FGF-17	CadherinE	KPCI	ERBB1	SCFsR	CK-MB	0.85	0.819	1.669	0.89
72	IL-17B	CadherinE	ERBB1	CalpainI	VEGF	METAP1	0.878	0.795	1.673	0.877
73	MMR	ERBB1	CadherinE	IMB1	RGM-C	METAP1	0.883	0.793	1.675	0.894
74	RGM-C	CadherinE	ERBB1	HSP90a	LGMN	VEGF	0.85	0.814	1.664	0.881
75	RGM-C	MK13	ERBB1	METAP1	CadherinE	MMR	0.869	0.805	1.673	0.896
76	CNDP1	CadherinE	CSK	ERBB1	VEGF	NACA	0.883	0.786	1.668	0.884
77	CadherinE	HSP90b	ERBB1	Proteinase-3	RGM-C	SCFsR	0.85	0.817	1.666	0.889
78	Prothrombin	CadherinE	ERBB1	HSP90b	RGM-C	VEGF	0.859	0.812	1.671	0.886
79	b-ECGF	CadherinE	ERBB1	CalpainI	HSP90b	CK-MB	0.845	0.826	1.671	0.887
80	ApoA-I	MMP-7	CadherinE	KPCI	SCFsR	LRIG3	0.869	0.802	1.671	0.885
81	RGM-C	CadherinE	ERBB1	CSK	BLC	MMP-7	0.836	0.824	1.659	0.883
82	BMP-1	ERBB1	HSP90a	RGM-C	CadherinE	CK-MB	0.822	0.845	1.667	0.896
83	HMG-1	KPCI	ERBB1	CadherinE	MMR	C9	0.859	0.81	1.669	0.884
84	RGM-C	HSP90b	ERBB1	SCFsR	CadherinE	CATC	0.864	0.786	1.65	0.879
85	RGM-C	CadherinE	CalpainI	CK-MB	CD30Ligand	ERBB1	0.869	0.81	1.678	0.903
86	Cadherin-6	CK-MB	CadherinE	ERBB1	KPCI	CNDP1	0.84	0.81	1.65	0.881
87	CadherinE	IGFBP-2	GAPDH, liver	CK-MB	MK13	Catalase	0.859	0.807	1.666	0.885
88	CathepsinH	RGM-C	METAP1	CK-MB	CadherinE	MMP-7	0.878	0.788	1.666	0.901
89	SCFsR	ERBB1	CalpainI	FGF-17	CadherinE	RGM-C	0.864	0.805	1.669	0.895
90	IL-17B	CadherinE	ERBB1	NAGK	CK-MB	RGM-C	0.831	0.84	1.671	0.891
91	SCFsR	ERBB1	CadherinE	IMB1	RGM-C	LRIG3	0.873	0.798	1.671	0.887
92	LGMN	CadherinE	ERBB1	C9	CSK	IGFBP-2	0.854	0.81	1.664	0.88
93	MEK1	RGM-C	ERBB1	CadherinE	METAP1	NAGK	0.878	0.795	1.673	0.885
94	NACA	CadherinE	ERBB1	METAP1	MMR	RGM-C	0.883	0.786	1.668	0.89
95	Proteinase-3	SCFsR	CadherinE	KPCI	MMP-7	CK-MB	0.854	0.812	1.666	0.885
96	CK-MB	MMP-7	CadherinE	Prothrombin	GAPDH, liver	SCFsR	0.869	0.802	1.671	0.897
97	b-ECGF	CalpainI	ERBB1	RGM-C	CadherinE	HSP90b	0.854	0.817	1.671	0.885
98	ApoA-I	RGM-C	HSP90a	ERBB1	CadherinE	CalpainI	0.869	0.802	1.671	0.897
99	BLC	CadherinE	METAP1	ERBB1	CK-MB	RGM-C	0.854	0.805	1.659	0.898
100	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	BMP-1	0.845	0.821	1.666	0.894

TABLE 5-continued

Marker	Count	Marker	Count
CadherinE	99	C9	6
ERBB1	84	BMP-1	6
RGM-C	63	BLC	6
CK-MB	49	ApoA-I	6
METAP1	24	b-ECGF	5
CalpainI	22	Prothrombin	5
SCFsR	19	Proteinase-3	5
KPCI	19	NACA	5
HSP90b	16	MK13	5
YES	15	MEK1	5
MMP-7	14	LGMN	5
CSK	11	IMB1	5
MMR	9	IL-17B	5
HSP90a	9	HMG-1	5
VEGF	8	FGF-17	5
IGFBP-2	8	CathepsinH	5
GAPDH, liver	8	Catalase	5
CNDP1	7	Cadherin-6	5
NAGK	6	CD30Ligand	5
LRIG3	6	CATC	5

TABLE 6

100 Panels of 7 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers				Sensitivity	Specificity	Sens. + Spec.	AUC
1	IGFBP-2	ERBB1	HSP90a	RGM-C	0.859	0.833	1.692	0.903
		CadherinE	SCFsR	ApoA-I				
2	BLC	CadherinE	METAP1	ERBB1	0.878	0.798	1.676	0.901
		CK-MB	RGM-C	MMP-7				
3	HSP90b	GAPDH, liver	ERBB1	CadherinE	0.873	0.817	1.69	0.891
		CK-MB	LRIG3	BMP-1				
4	CK-MB	CadherinE	KPCI	C9	0.892	0.807	1.699	0.891
		SCFsR	CSK	LRIG3				
5	SCFsR	ERBB1	CadherinE	CalpainI	0.869	0.802	1.671	0.88
		HSP90b	RGM-C	CATC				
6	CD30Ligand	KPCI	ERBB1	SCFsR	0.878	0.814	1.692	0.89
		CadherinE	CK-MB	CalpainI				
7	YES	CNDP1	HSP90a	ERBB1	0.883	0.817	1.699	0.902
		RGM-C	CadherinE	SCFsR				
8	MMP-7	ERBB1	CadherinE	CalpainI	0.85	0.831	1.681	0.895
		CK-MB	RGM-C	Cadherin-6				
9	Catalase	CalpainI	CadherinE	ERBB1	0.873	0.817	1.69	0.903
		RGM-C	CK-MB	CNDP1				
10	MMR	SCFsR	CadherinE	GAPDH, liver	0.906	0.786	1.692	0.898
		RGM-C	Prothrombin	CathepsinH				
11	SCFsR	ERBB1	RGM-C	HSP90a	0.887	0.805	1.692	0.896
		CadherinE	FGF-17	CalpainI				
12	HMG-1	RGM-C	ERBB1	CadherinE	0.859	0.843	1.702	0.899
		CK-MB	YES	SCFsR				
13	IL-17B	CadherinE	ERBB1	METAP1	0.883	0.81	1.692	0.894
		CK-MB	HSP90b	SCFsR				
14	SCFsR	ERBB1	CadherinE	IMB1	0.887	0.807	1.694	0.9
		CSK	CNDP1	CK-MB				
15	LGMN	HSP90b	CadherinE	ERBB1	0.873	0.807	1.68	0.886
		RGM-C	SCFsR	VEGF				
16	MEK1	RGM-C	ERBB1	CadherinE	0.883	0.814	1.697	0.9
		CK-MB	METAP1	NAGK				
17	MMR	ERBB1	METAP1	CK-MB	0.887	0.802	1.69	0.909
		CadherinE	RGM-C	MK13				
18	RGM-C	METAP1	SCFsR	ERBB1	0.906	0.798	1.704	0.886
		HSP90a	CadherinE	NACA				
19	CK-MB	CNDP1	KPCI	CadherinE	0.864	0.824	1.688	0.887
		SCFsR	Proteinase-3	LRIG3				
20	b-ECGF	CadherinE	ERBB1	METAP1	0.883	0.817	1.699	0.901
		RGM-C	CK-MB	YES				
21	YES	CadherinE	KPCI	CK-MB	0.873	0.812	1.685	0.892
		ERBB1	HSP90a	ApoA-I				
22	RGM-C	METAP1	SCFsR	ERBB1	0.883	0.793	1.675	0.889
		HSP90a	CadherinE	BLC				
23	RGM-C	KPCI	SCFsR	BMP-1	0.873	0.814	1.688	0.889
		CadherinE	CK-MB	HSP90a				
24	RGM-C	CadherinE	KPCI	CK-MB	0.878	0.817	1.695	0.89
		HSP90a	SCFsR	C9				

TABLE 6-continued

25	METAP1	HSP90b	CadherinE	ERBB1	0.887	0.774	1.661	0.884
		RGM-C	SCFsR	CATC				
26	CD30Ligand	GAPDH, liver	ERBB1	CK-MB	0.864	0.826	1.69	0.905
		CadherinE	RGM-C	YES				
27	RGM-C	HSP90b	ERBB1	SCFsR	0.869	0.805	1.673	0.886
		CadherinE	Cadherin-6	CNDP1				
28	Catalase	CalpainI	CadherinE	ERBB1	0.869	0.817	1.685	0.888
		RGM-C	CK-MB	KPCI				
29	CathepsinH	ERBB1	CadherinE	METAP1	0.883	0.805	1.687	0.904
		YES	RGM-C	CK-MB				
30	CK-MB	ERBB1	CadherinE	GAPDH, liver	0.873	0.817	1.69	0.902
		FGF-17	MMP-7	METAP1				
31	HMG-1	CK-MB	CadherinE	ERBB1	0.873	0.826	1.699	0.905
		HSP90a	RGM-C	YES				
32	HMG-1	CK-MB	CadherinE	ERBB1	0.859	0.836	1.695	0.905
		HSP90a	RGM-C	IGFBP-2				
33	METAP1	HSP90b	CadherinE	ERBB1	0.892	0.8	1.692	0.892
		RGM-C	SCFsR	IL-17B				
34	SCFsR	ERBB1	CadherinE	METAP1	0.901	0.793	1.694	0.9
		IMB1	RGM-C	MMP-7				
35	RGM-C	HSP90b	ERBB1	SCFsR	0.854	0.821	1.676	0.886
		CadherinE	MEK1	LGMN				
36	CK-MB	MMP-7	CadherinE	KPCI	0.873	0.814	1.688	0.894
		SCFsR	CSK	MK13				
37	NACA	CadherinE	ERBB1	METAP1	0.897	0.805	1.701	0.891
		CK-MB	MMR	LRIG3				
38	SCFsR	ERBB1	CadherinE	CalpainI	0.892	0.81	1.702	0.902
		RGM-C	NAGK	CK-MB				
39	Proteinase-3	GAPDH, liver	ERBB1	CadherinE	0.854	0.829	1.683	0.901
		CK-MB	YES	SCFsR				
40	RGM-C	CadherinE	KPCI	CK-MB	0.859	0.829	1.688	0.887
		SCFsR	CD30Ligand	Prothrombin				
41	VEGF	RGM-C	ERBB1	METAP1	0.892	0.802	1.694	0.905
		CK-MB	CadherinE	YES				
42	b-ECGF	CadherinE	ERBB1	HSP90b	0.892	0.8	1.692	0.895
		RGM-C	SCFsR	METAP1				
43	METAP1	GAPDH, liver	MMP-7	CadherinE	0.892	0.793	1.685	0.894
		ERBB1	ApoA-I	YES				
44	CalpainI	HSP90a	CK-MB	RGM-C	0.85	0.824	1.674	0.892
		ERBB1	CadherinE	BLC				
45	VEGF	RGM-C	ERBB1	METAP1	0.887	0.798	1.685	0.895
		CadherinE	CalpainI	BMP-1				
46	CK-MB	CadherinE	KPCI	C9	0.897	0.795	1.692	0.896
		SCFsR	CSK	MMP-7				
47	KPCI	CalpainI	CadherinE	CK-MB	0.869	0.79	1.659	0.879
		IGFBP-2	ERBB1	CATC				
48	RGM-C	CK-MB	ERBB1	IMB1	0.873	0.8	1.673	0.888
		CadherinE	SCFsR	Cadherin-6				
49	SCFsR	ERBB1	CadherinE	METAP1	0.897	0.788	1.685	0.903
		RGM-C	MMR	Catalase				
50	CathepsinH	ERBB1	CadherinE	METAP1	0.892	0.795	1.687	0.889
		YES	RGM-C	GAPDH, liver				
51	CK-MB	ERBB1	CadherinE	NAGK	0.854	0.833	1.688	0.896
		FGF-17	RGM-C	SCFsR				
52	CalpainI	ERBB1	CadherinE	NAGK	0.869	0.819	1.688	0.898
		CK-MB	IL-17B	RGM-C				
53	VEGF	CalpainI	CadherinE	CK-MB	0.859	0.817	1.676	0.893
		ERBB1	RGM-C	LGMN				
54	MEK1	RGM-C	ERBB1	CadherinE	0.864	0.824	1.688	0.902
		METAP1	YES	CK-MB				
55	SCFsR	ERBB1	CadherinE	METAP1	0.887	0.8	1.687	0.901
		RGM-C	MMR	MK13				
56	CK-MB	MMP-7	CadherinE	NACA	0.901	0.795	1.697	0.897
		METAP1	RGM-C	ERBB1				
57	MMP-7	ERBB1	CadherinE	CalpainI	0.859	0.824	1.683	0.894
		CK-MB	Proteinase-3	YES				
58	MMR	ERBB1	METAP1	CK-MB	0.901	0.786	1.687	0.9
		CadherinE	YES	Prothrombin				
59	b-ECGF	CK-MB	NAGK	CadherinE	0.869	0.821	1.69	0.893
		CalpainI	ERBB1	CD30Ligand				
60	CadherinE	IGFBP-2	HSP90a	CK-MB	0.84	0.843	1.683	0.907
		ERBB1	RGM-C	ApoA-I				
61	SCFsR	ERBB1	CadherinE	CalpainI	0.859	0.814	1.673	0.891
		RGM-C	CK-MB	BLC				
62	METAP1	IMB1	ERBB1	CadherinE	0.901	0.783	1.685	0.886
		YES	BMP-1	RGM-C				
63	CadherinE	METAP1	CK-MB	C9	0.883	0.807	1.69	0.907
		ERBB1	IGFBP-2	SCFsR				
64	YES	CadherinE	ERBB1	RGM-C	0.878	0.781	1.659	0.876
		NAGK	METAP1	CATC				

TABLE 6-continued

65	CadherinE	IGFBP-2	HSP90a	CK-MB	0.845	0.826	1.671	0.891
		ERBB1	RGM-C	Cadherin-6				
66	Catalase	HSP90b	ERBB1	CadherinE	0.878	0.802	1.68	0.893
		CK-MB	YES	LRIG3				
67	CathepsinH	CSK	ERBB1	RGM-C	0.873	0.812	1.685	0.9
		CadherinE	SCFsR	IGFBP-2				
68	RGM-C	CK-MB	ERBB1	METAP1	0.878	0.81	1.687	0.893
		FGF-17	CadherinE	HSP90b				
69	CadherinE	HSP90b	ERBB1	HMG-1	0.878	0.821	1.699	0.897
		RGM-C	SCFsR	CK-MB				
70	IL-17B	CK-MB	KPCI	CadherinE	0.883	0.805	1.687	0.888
		ERBB1	SCFsR	NAGK				
71	MMP-7	ERBB1	CadherinE	LGMN	0.859	0.817	1.676	0.894
		CSK	YES	CK-MB				
72	MEK1	RGM-C	ERBB1	CadherinE	0.864	0.821	1.685	0.902
		CK-MB	CalpainI	CSK				
73	RGM-C	CadherinE	KPCI	CK-MB	0.873	0.812	1.685	0.887
		HSP90a	IGFBP-2	MK13				
74	MMP-7	ERBB1	YES	METAP1	0.897	0.793	1.69	0.89
		CadherinE	NACA	CK-MB				
75	SCFsR	ERBB1	CadherinE	CalpainI	0.859	0.824	1.683	0.892
		RGM-C	MEK1	Proteinase-3				
76	Prothrombin	CadherinE	ERBB1	CalpainI	0.854	0.831	1.685	0.883
		YES	CK-MB	KPCI				
77	b-ECGF	CadherinE	ERBB1	HSP90a	0.873	0.817	1.69	0.901
		CalpainI	CK-MB	RGM-C				
78	METAP1	HSP90b	CadherinE	ERBB1	0.878	0.805	1.683	0.884
		RGM-C	ApoA-I	YES				
79	BLC	CadherinE	METAP1	ERBB1	0.869	0.805	1.673	0.899
		CK-MB	RGM-C	SCFsR				
80	RGM-C	CadherinE	ERBB1	CSK	0.85	0.833	1.683	0.894
		BMP-1	CK-MB	LRIG3				
81	CK-MB	IGFBP-2	CSK	CadherinE	0.887	0.8	1.687	0.896
		KPCI	SCFsR	C9				
82	GAPDH, liver	CalpainI	ERBB1	CadherinE	0.859	0.795	1.654	0.89
		CK-MB	IGFBP-2	CATC				
83	SCFsR	ERBB1	CadherinE	METAP1	0.883	0.807	1.69	0.894
		CD30Ligand	RGM-C	HSP90b				
84	b-ECGF	CalpainI	ERBB1	RGM-C	0.845	0.824	1.669	0.892
		CadherinE	CK-MB	Cadherin-6				
85	Catalase	CadherinE	ERBB1	KPCI	0.883	0.798	1.68	0.891
		YES	SCFsR	CNDP1				
86	RGM-C	CadherinE	KPCI	CK-MB	0.883	0.802	1.685	0.887
		HSP90a	SCFsR	CathepsinH				
87	RGM-C	CK-MB	ERBB1	METAP1	0.883	0.805	1.687	0.898
		FGF-17	CadherinE	NAGK				
88	RGM-C	CadherinE	KPCI	CK-MB	0.869	0.819	1.688	0.893
		SCFsR	ERBB1	HMG-1				
89	IL-17B	GAPDH, liver	ERBB1	CK-MB	0.854	0.831	1.685	0.898
		CadherinE	RGM-C	YES				
90	RGM-C	CK-MB	ERBB1	IMB1	0.878	0.814	1.692	0.898
		CadherinE	SCFsR	CNDP1				
91	CNDP1	ERBB1	CadherinE	KPCI	0.873	0.802	1.676	0.885
		SCFsR	YES	LGMN				
92	CadherinE	MK13	KPCI	CK-MB	0.883	0.8	1.683	0.897
		MMR	ERBB1	CSK				
93	NACA	CadherinE	ERBB1	METAP1	0.915	0.774	1.689	0.896
		MMR	RGM-C	SCFsR				
94	CD30Ligand	KPCI	ERBB1	SCFsR	0.864	0.817	1.681	0.889
		CadherinE	CK-MB	Proteinase-3				
95	CadherinE	METAP1	CK-MB	HSP90b	0.869	0.817	1.685	0.884
		ERBB1	YES	Prothrombin				
96	YES	CadherinE	ERBB1	CSK	0.864	0.829	1.692	0.906
		VEGF	CK-MB	RGM-C				
97	METAP1	HSP90b	CadherinE	ERBB1	0.878	0.805	1.683	0.895
		RGM-C	ApoA-I	IGFBP-2				
98	RGM-C	METAP1	SCFsR	ERBB1	0.869	0.805	1.673	0.899
		CK-MB	CadherinE	BLC				
99	LRIG3	CadherinE	METAP1	HSP90b	0.873	0.81	1.683	0.892
		CK-MB	BMP-1	SCFsR				
100	SCFsR	MMP-7	METAP1	b-ECGF	0.892	0.795	1.687	0.901
		CadherinE	C9	CK-MB				

Marker	Count	Marker	Count
CadherinE	100	CD30Ligand	6
ERBB1	87	C9	6
CK-MB	71	BMP-1	6
RGM-C	68	BLC	6
SCFsR	50	ApoA-I	6

TABLE 6-continued

METAP1	38	VEGF	5
YES	26	Prothrombin	5
KPCI	21	Proteinase-3	5
CalpainI	21	NACA	5
HSP90b	17	MK13	5
HSP90a	16	MEK1	5
MMP-7	12	LGMN	5
IGFBP-2	11	IMB1	5
CSK	11	IL-17B	5
GAPDH, liver	9	HMG-1	5
NAGK	8	FGF-17	5
MMR	8	CathepsinH	5
CNDP1	8	Catalase	5
LRIG3	7	Cadherin-6	5
b-ECGF	6	CATC	5

TABLE 7

100 Panels of 8 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers					Sensitivity	Specificity	Sens. + Spec.	AUC
1	CadherinE	IGFBP-2	HSP90a	CK-MB		0.892	0.819	1.711	0.914
	ERBB1	RGM-C	ApoA-I	CSK					
2	RGM-C	METAP1	SCFsR	ERBB1		0.883	0.812	1.695	0.897
	HSP90a	CadherinE	BLC	CK-MB					
3	RGM-C	METAP1	SCFsR	ERBB1		0.892	0.81	1.702	0.909
	YES	CadherinE	CK-MB	BMP-1					
4	SCFsR	MMP-7	CadherinE	KPCI		0.906	0.802	1.708	0.897
	METAP1	RGM-C	CK-MB	C9					
5	CK-MB	IGFBP-2	CSK	CadherinE		0.869	0.812	1.68	0.892
	RGM-C	ERBB1	YES	CATC					
6	RGM-C	METAP1	SCFsR	ERBB1		0.915	0.805	1.72	0.909
	YES	CadherinE	CD30Ligand	CK-MB					
7	SCFsR	ERBB1	HSP90a	YES		0.911	0.798	1.708	0.899
	CadherinE	IMB1	RGM-C	CNDP1					
8	b-ECGF	CadherinE	ERBB1	HSP90b		0.878	0.802	1.68	0.885
	RGM-C	SCFsR	HSP90a	Cadherin-6					
9	RGM-C	CadherinE	KPCI	CK-MB		0.901	0.812	1.713	0.893
	HSP90a	ERBB1	CalpainI	SCFsR					
10	CK-MB	IGFBP-2	KPCI	CadherinE		0.897	0.8	1.697	0.891
	METAP1	SCFsR	CNDP1	Catalase					
11	CathepsinH	CSK	ERBB1	RGM-C		0.906	0.8	1.706	0.898
	CadherinE	SCFsR	KPCI	CK-MB					
12	CadherinE	METAP1	CK-MB	HSP90b		0.892	0.817	1.709	0.889
	ERBB1	YES	FGF-17	b-ECGF					
13	CSK	CadherinE	CK-MB	GAPDH, liver		0.901	0.821	1.723	0.916
	ERBB1	MMR	YES	RGM-C					
14	CadherinE	IGFBP-2	HSP90a	CK-MB		0.873	0.831	1.704	0.907
	ERBB1	RGM-C	ApoA-I	HMG-1					
15	IL-17B	CadherinE	ERBB1	METAP1		0.901	0.805	1.706	0.903
	CK-MB	RGM-C	YES	SCFsR					
16	RGM-C	HSP90b	ERBB1	SCFsR		0.864	0.821	1.685	0.895
	CadherinE	CK-MB	LRIG3	LGMN					
17	SCFsR	ERBB1	CadherinE	CalpainI		0.878	0.829	1.707	0.902
	RGM-C	NAGK	CK-MB	MEK1					
18	IGFBP-2	MMP-7	CadherinE	METAP1		0.897	0.81	1.706	0.908
	SCFsR	RGM-C	MK13	CK-MB					
19	MMP-7	ERBB1	YES	CSK		0.93	0.779	1.708	0.899
	CadherinE	RGM-C	NACA	SCFsR					
20	RGM-C	CadherinE	ERBB1	GAPDH, liver		0.873	0.829	1.702	0.906
	SCFsR	CK-MB	Proteinase-3	YES					
21	CadherinE	SCFsR	GAPDH, liver	MEK1		0.901	0.802	1.704	0.901
	CK-MB	RGM-C	CathepsinH	Prothrombin					
22	RGM-C	METAP1	SCFsR	ERBB1		0.906	0.812	1.718	0.908
	YES	CadherinE	CK-MB	VEGF					
23	RGM-C	CK-MB	ERBB1	METAP1		0.892	0.802	1.694	0.893
	FGF-17	CadherinE	NAGK	BLC					
24	RGM-C	BMP-1	ERBB1	METAP1		0.883	0.817	1.699	0.888
	CadherinE	HSP90b	SCFsR	IMB1					
25	CSK	IGFBP-2	CadherinE	ERBB1		0.878	0.829	1.707	0.903
	C9	NAGK	CK-MB	YES					
26	CK-MB	MMP-7	METAP1	RGM-C		0.873	0.805	1.678	0.893
	CadherinE	MK13	ERBB1	CATC					
27	CD30Ligand	RGM-C	ERBB1	KPCI		0.897	0.814	1.711	0.897
	CadherinE	CK-MB	SCFsR	CalpainI					

TABLE 7-continued

28	CD30Ligand	RGM-C	ERBB1	KPCI	0.869	0.81	1.678	0.89
	CadherinE	CK-MB	SCFsR	Cadherin-6				
29	MEK1	RGM-C	ERBB1	CadherinE	0.883	0.81	1.692	0.899
	METAP1	YES	CK-MB	Catalase				
30	b-ECGF	CalpainI	ERBB1	RGM-C	0.883	0.821	1.704	0.902
	CadherinE	HMG-1	CK-MB	SCFsR				
31	RGM-C	CK-MB	ERBB1	IMB1	0.887	0.817	1.704	0.898
	CadherinE	SCFsR	CNDP1	IL-17B				
32	HSP90b	KPCI	ERBB1	CadherinE	0.869	0.814	1.683	0.885
	RGM-C	SCFsR	MMR	LGMN				
33	SCFsR	ERBB1	CadherinE	CalpainI	0.892	0.814	1.706	0.905
	RGM-C	HSP90a	CK-MB	LRIG3				
34	RGM-C	METAP1	SCFsR	ERBB1	0.915	0.788	1.704	0.897
	YES	CadherinE	MMP-7	NACA				
35	CadherinE	GAPDH, liver	HSP90a	SCFsR	0.878	0.819	1.697	0.901
	ERBB1	RGM-C	IGFBP-2	Proteinase-3				
36	SCFsR	MMP-7	CadherinE	KPCI	0.906	0.798	1.704	0.894
	Prothrombin	RGM-C	CK-MB	HSP90a				
37	CK-MB	ERBB1	CadherinE	NAGK	0.887	0.819	1.706	0.907
	CSK	YES	RGM-C	VEGF				
38	MMR	CSK	CadherinE	CK-MB	0.892	0.814	1.706	0.919
	RGM-C	ERBB1	GAPDH, liver	ApoA-I				
39	BLC	CadherinE	METAP1	ERBB1	0.897	0.798	1.694	0.903
	CK-MB	RGM-C	MMP-7	GAPDH, liver				
40	YES	CadherinE	MMP-7	HMG-1	0.873	0.824	1.697	0.893
	ERBB1	CK-MB	KPCI	BMP-1				
41	YES	C9	ERBB1	CSK	0.873	0.831	1.704	0.901
	CK-MB	CadherinE	NAGK	FGF-17				
42	RGM-C	CK-MB	ERBB1	METAP1	0.887	0.79	1.678	0.888
	FGF-17	CadherinE	NAGK	CATC				
43	CNDP1	ERBB1	CadherinE	KPCI	0.869	0.81	1.678	0.891
	SCFsR	RGM-C	CK-MB	Cadherin-6				
44	YES	HSP90b	CadherinE	ERBB1	0.887	0.805	1.692	0.897
	CSK	RGM-C	CK-MB	Catalase				
45	CathepsinH	RGM-C	METAP1	CK-MB	0.901	0.8	1.701	0.907
	CadherinE	ERBB1	SCFsR	YES				
46	METAP1	HSP90b	CadherinE	ERBB1	0.892	0.81	1.702	0.9
	RGM-C	IL-17B	CK-MB	SCFsR				
47	SCFsR	ERBB1	CadherinE	METAP1	0.887	0.795	1.683	0.892
	RGM-C	MMR	HSP90b	LGMN				
48	YES	CK-MB	ERBB1	CadherinE	0.883	0.814	1.697	0.907
	GAPDH, liver	LRIG3	MMR	CSK				
49	YES	CK-MB	ERBB1	METAP1	0.897	0.807	1.704	0.907
	RGM-C	CadherinE	MK13	MMR				
50	SCFsR	ERBB1	CadherinE	CalpainI	0.901	0.8	1.701	0.885
	RGM-C	HSP90a	b-ECGF	NACA				
51	CadherinE	METAP1	CK-MB	HSP90b	0.892	0.802	1.694	0.897
	ERBB1	RGM-C	SCFsR	Proteinase-3				
52	YES	NAGK	CadherinE	ERBB1	0.906	0.795	1.701	0.898
	CK-MB	MMP-7	METAP1	Prothrombin				
53	VEGF	METAP1	ERBB1	YES	0.906	0.798	1.704	0.902
	CadherinE	CK-MB	NAGK	RGM-C				
54	CadherinE	IGFBP-2	METAP1	ERBB1	0.906	0.793	1.699	0.911
	RGM-C	HSP90a	CK-MB	ApoA-I				
55	RGM-C	CadherinE	ERBB1	GAPDH, liver	0.873	0.819	1.692	0.904
	SCFsR	CK-MB	CSK	BLC				
56	CK-MB	IGFBP-2	KPCI	CadherinE	0.892	0.805	1.697	0.895
	METAP1	SCFsR	CNDP1	BMP-1				
57	CSK	SCFsR	CadherinE	C9	0.901	0.802	1.704	0.904
	ERBB1	IGFBP-2	CK-MB	IMB1				
58	RGM-C	METAP1	SCFsR	ERBB1	0.897	0.781	1.678	0.895
	YES	CadherinE	CK-MB	CATC				
59	CD30Ligand	RGM-C	ERBB1	KPCI	0.887	0.819	1.706	0.899
	CadherinE	CK-MB	SCFsR	YES				
60	MMR	ERBB1	METAP1	CK-MB	0.864	0.81	1.673	0.891
	CadherinE	RGM-C	MK13	Cadherin-6				
61	CadherinE	IGFBP-2	METAP1	ERBB1	0.892	0.8	1.692	0.894
	CK-MB	Catalase	RGM-C	KPCI				
62	CSK	KPCI	ERBB1	CadherinE	0.897	0.802	1.699	0.892
	SCFsR	YES	CNDP1	CathepsinH				
63	MMR	SCFsR	CadherinE	CalpainI	0.878	0.821	1.699	0.908
	ERBB1	RGM-C	CK-MB	HMG-1				
64	SCFsR	ERBB1	CadherinE	METAP1	0.906	0.795	1.701	0.897
	IMB1	RGM-C	MMP-7	IL-17B				
65	YES	CK-MB	ERBB1	CadherinE	0.85	0.831	1.681	0.893
	GAPDH, liver	VEGF	BMP-1	LGMN				
66	CadherinE	IGFBP-2	KPCI	MMR	0.887	0.81	1.697	0.894
	SCFsR	GAPDH, liver	CK-MB	LRIG3				
67	METAP1	GAPDH, liver	MMP-7	CadherinE	0.892	0.812	1.704	0.908
	ERBB1	CK-MB	RGM-C	MEK1				

TABLE 7-continued

68	NACA	CadherinE	ERBB1	CSK	0.92	0.781	1.701	0.899
	RGM-C	MMR	YES	SCFsR				
69	Proteinase-3	SCFsR	CadherinE	KPCI	0.878	0.814	1.692	0.891
	ERBB1	RGM-C	CK-MB	CathepsinH				
70	RGM-C	CadherinE	CalpainI	VEGF	0.883	0.817	1.699	0.903
	ERBB1	CD30Ligand	CK-MB	Prothrombin				
71	IGFBP-2	ERBB1	HSP90a	RGM-C	0.892	0.805	1.697	0.908
	CadherinE	SCFsR	ApoA-I	CSK				
72	CadherinE	METAP1	CK-MB	C9	0.878	0.814	1.692	0.896
	ERBB1	IGFBP-2	SCFsR	BLC				
73	MMR	ERBB1	GAPDH, liver	CadherinE	0.901	0.776	1.678	0.895
	RGM-C	CSK	SCFsR	CATC				
74	RGM-C	HSP90b	ERBB1	SCFsR	0.869	0.805	1.673	0.895
	CadherinE	CK-MB	LRIG3	Cadherin-6				
75	CadherinE	IGFBP-2	METAP1	ERBB1	0.892	0.8	1.692	0.9
	CK-MB	Catalase	RGM-C	HSP90b				
76	RGM-C	FGF-17	ERBB1	CalpainI	0.892	0.812	1.704	0.901
	CadherinE	CK-MB	SCFsR	NAGK				
77	HMG-1	CalpainI	ERBB1	CadherinE	0.873	0.824	1.697	0.908
	CK-MB	RGM-C	MMP-7	SCFsR				
78	IL-17B	GAPDH, liver	ERBB1	CK-MB	0.883	0.817	1.699	0.901
	CadherinE	RGM-C	CalpainI	SCFsR				
79	YES	CadherinE	ERBB1	RGM-C	0.869	0.812	1.68	0.897
	LGMN	HSP90a	ApoA-I	CK-MB				
80	MEK1	RGM-C	ERBB1	CadherinE	0.897	0.807	1.704	0.905
	METAP1	YES	CK-MB	SCFsR				
81	CK-MB	MMP-7	METAP1	RGM-C	0.883	0.819	1.702	0.909
	CadherinE	MK13	ERBB1	IGFBP-2				
82	NACA	CadherinE	ERBB1	METAP1	0.892	0.807	1.699	0.896
	CK-MB	MMR	RGM-C	Prothrombin				
83	Proteinase-3	GAPDH, liver	ERBB1	CadherinE	0.845	0.845	1.69	0.896
	CK-MB	YES	MEK1	C9				
84	b-ECGF	CadherinE	ERBB1	METAP1	0.906	0.807	1.713	0.902
	RGM-C	CK-MB	HSP90b	SCFsR				
85	CadherinE	IGFBP-2	METAP1	ERBB1	0.892	0.798	1.69	0.9
	CK-MB	Catalase	RGM-C	BLC				
86	RGM-C	KPCI	SCFsR	BMP-1	0.878	0.817	1.695	0.888
	CadherinE	CK-MB	GAPDH, liver	HSP90a				
87	MMP-7	ERBB1	YES	METAP1	0.906	0.769	1.675	0.88
	CadherinE	NACA	CK-MB	CATC				
88	CD30Ligand	KPCI	ERBB1	SCFsR	0.901	0.805	1.706	0.897
	CadherinE	CK-MB	CSK	YES				
89	RGM-C	CadherinE	KPCI	CK-MB	0.869	0.8	1.669	0.881
	HSP90a	SCFsR	C9	Cadherin-6				
90	CK-MB	CNDP1	KPCI	CadherinE	0.897	0.8	1.697	0.891
	SCFsR	CSK	CathepsinH	LRIG3				
91	RGM-C	CK-MB	ERBB1	METAP1	0.906	0.798	1.704	0.904
	FGF-17	CadherinE	NAGK	SCFsR				
92	MK13	CalpainI	CadherinE	ERBB1	0.873	0.824	1.697	0.904
	MMR	RGM-C	HMG-1	CK-MB				
93	CK-MB	CNDP1	KPCI	CadherinE	0.887	0.812	1.699	0.886
	SCFsR	Prothrombin	IL-17B	YES				
94	IMB1	HSP90a	ERBB1	CadherinE	0.887	0.817	1.704	0.888
	RGM-C	SCFsR	KPCI	CK-MB				
95	YES	C9	ERBB1	CSK	0.873	0.807	1.68	0.892
	CK-MB	CadherinE	LGMN	HSP90a				
96	MMR	SCFsR	CadherinE	CalpainI	0.869	0.821	1.69	0.902
	ERBB1	RGM-C	CK-MB	Proteinase-3				
97	RGM-C	CadherinE	ERBB1	GAPDH, liver	0.873	0.826	1.699	0.905
	SCFsR	CK-MB	CalpainI	VEGF				
98	CK-MB	SCFsR	METAP1	CadherinE	0.915	0.79	1.706	0.9
	MMP-7	HSP90b	b-ECGF	RGM-C				
99	RGM-C	METAP1	SCFsR	ERBB1	0.901	0.795	1.697	0.909
	YES	CadherinE	MMP-7	ApoA-I				
100	CSK	CadherinE	CK-MB	GAPDH, liver	0.873	0.812	1.685	0.901
	ERBB1	YES	RGM-C	BLC				

Marker	Count	Marker	Count
CadherinE	100	ApoA-I	7
ERBB1	88	b-ECGF	6
CK-MB	85	VEGF	6
RGM-C	81	Prothrombin	6
SCFsR	64	Proteinase-3	6
METAP1	41	NACA	6
YES	36	MK13	6
KPCI	22	MEK1	6
CSK	21	LRIG3	6
IGFBP-2	17	LGMN	6
HSP90a	17	IMB1	6

TABLE 7-continued

GAPDH, liver	17	IL-17B	6
MMP-7	16	HMG-1	6
MMR	14	FGF-17	6
CalpainI	14	CathepsinH	6
HSP90b	13	Catalase	6
NAGK	10	Cadherin-6	6
CNDP1	8	CD30Ligand	6
C9	8	CATC	6
BLC	7	BMP-1	6

TABLE 8

100 Panels of 9 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers					Sensitivity	Specificity	Sens. + Spec.	AUC
1	CSK	IMB1	ERBB1	CadherinE	RGM-C	0.906	0.807	1.713	0.905
		MMR	YES	CK-MB	ApoA-I				
2	METAP1	CalpainI	ERBB1	CadherinE	MMP-7	0.906	0.802	1.708	0.901
		RGM-C	CK-MB	SCFsR	BLC				
3	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.883	0.831	1.714	0.914
		YES	BMP-1	RGM-C	MMR				
4	RGM-C	C9	ERBB1	CadherinE	METAP1	0.906	0.812	1.718	0.913
		YES	CK-MB	MMP-7	SCFsR				
5	CathepsinH	RGM-C	METAP1	CK-MB	CadherinE	0.906	0.793	1.699	0.895
		ERBB1	SCFsR	YES	CATC				
6	YES	CadherinE	GAPDH, liver	MMP-7	SCFsR	0.897	0.814	1.711	0.906
		CK-MB	RGM-C	CSK	CD30Ligand				
7	YES	CadherinE	ERBB1	CSK	VEGF	0.906	0.807	1.713	0.901
		RGM-C	CalpainI	CNDP1	MMP-7				
8	CSK	KPCI	ERBB1	CadherinE	CK-MB	0.883	0.805	1.687	0.893
		RGM-C	SCFsR	MMR	Cadherin-6				
9	RGM-C	METAP1	SCFsR	ERBB1	YES	0.911	0.798	1.708	0.912
		CadherinE	CK-MB	Catalase	MMP-7				
10	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.911	0.817	1.727	0.897
		CK-MB	YES	ERBB1	FGF-17				
11	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.887	0.826	1.714	0.908
		MMR	YES	RGM-C	HMG-1				
12	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.915	0.814	1.73	0.898
		CadherinE	IGFBP-2	KPCI	CK-MB				
13	CadherinE	METAP1	CK-MB	HSP90b	ERBB1	0.906	0.812	1.718	0.897
		YES	SCFsR	RGM-C	HSP90a				
14	IL-17B	CadherinE	ERBB1	METAP1	CK-MB	0.906	0.81	1.716	0.904
		RGM-C	GAPDH, liver	MMP-7	YES				
15	YES	CadherinE	CalpainI	ERBB1	CK-MB	0.878	0.817	1.695	0.895
		RGM-C	SCFsR	CD30Ligand	LGMN				
16	CK-MB	SCFsR	METAP1	CadherinE	MMP-7	0.915	0.8	1.715	0.901
		HSP90b	RGM-C	LRIG3	b-ECGF				
17	b-ECGF	CK-MB	NAGK	CadherinE	CalpainI	0.883	0.831	1.714	0.901
		ERBB1	SCFsR	RGM-C	MEK1				
18	CK-MB	MMP-7	METAP1	RGM-C	CadherinE	0.892	0.824	1.716	0.912
		MK13	ERBB1	SCFsR	IGFBP-2				
19	MMP-7	ERBB1	YES	METAP1	CadherinE	0.915	0.8	1.715	0.902
		NACA	CK-MB	SCFsR	RGM-C				
20	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.906	0.805	1.711	0.895
		CK-MB	YES	ERBB1	Proteinase-3				
21	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.901	0.814	1.716	0.913
		MMR	YES	RGM-C	Prothrombin				
22	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	0.906	0.807	1.713	0.913
		CSK	SCFsR	YES	ApoA-I				
23	CK-MB	SCFsR	METAP1	CadherinE	ERBB1	0.892	0.81	1.702	0.901
		IGFBP-2	RGM-C	NAGK	BLC				
24	SCFsR	MMP-7	METAP1	b-ECGF	CadherinE	0.915	0.798	1.713	0.895
		HSP90b	RGM-C	GAPDH, liver	BMP-1				
25	RGM-C	C9	ERBB1	CadherinE	METAP1	0.92	0.795	1.715	0.908
		SCFsR	CK-MB	NAGK	YES				
26	CK-MB	ERBB1	CadherinE	NAGK	CSK	0.887	0.807	1.694	0.896
		YES	RGM-C	IGFBP-2	CATC				
27	SCFsR	ERBB1	HSP90a	YES	CadherinE	0.911	0.802	1.713	0.896
		IMB1	RGM-C	CNDP1	HMG-1				
28	b-ECGF	CadherinE	ERBB1	METAP1	RGM-C	0.897	0.79	1.687	0.892
		CK-MB	HSP90b	SCFsR	Cadherin-6				
29	CathepsinH	CSK	ERBB1	RGM-C	CadherinE	0.92	0.788	1.708	0.893
		SCFsR	KPCI	Catalase	YES				
30	METAP1	GAPDH, liver	MMP-7	CadherinE	CK-MB	0.915	0.812	1.727	0.913
		RGM-C	FGF-17	ERBB1	SCFsR				

TABLE 8-continued

31	IL-17B	CK-MB	KPCI	CadherinE	ERBB1	0.892	0.819	1.711	0.896
		CalpainI	SCFsR	CNDP1	RGM-C				
32	YES	CadherinE	ERBB1	CSK	SCFsR	0.897	0.798	1.694	0.901
		RGM-C	MMP-7	GAPDH, liver	LGMN				
33	RGM-C	HSP90b	ERBB1	SCFsR	CadherinE	0.911	0.8	1.711	0.906
		YES	CK-MB	CSK	LRIG3				
34	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	0.887	0.826	1.714	0.909
		CK-MB	CSK	MEK1	VEGF				
35	SCFsR	ERBB1	CadherinE	METAP1	RGM-C	0.892	0.817	1.709	0.911
		MMR	MK13	IGFBP-2	CK-MB				
36	RGM-C	NACA	ERBB1	CadherinE	HSP90a	0.915	0.8	1.715	0.895
		METAP1	CK-MB	YES	SCFsR				
37	MMP-7	ERBB1	YES	METAP1	CadherinE	0.911	0.798	1.708	0.895
		NACA	CK-MB	SCFsR	Proteinase-3				
38	CathepsinH	CSK	ERBB1	RGM-C	CadherinE	0.901	0.812	1.713	0.898
		SCFsR	KPCI	CK-MB	Prothrombin				
39	MMR	CSK	CadherinE	CK-MB	RGM-C	0.897	0.812	1.709	0.901
		ERBB1	KPCI	ApoA-I	YES				
40	RGM-C	CK-MB	ERBB1	METAP1	FGF-17	0.897	0.805	1.701	0.897
		CadherinE	NAGK	BLC	SCFsR				
41	RGM-C	BMP-1	ERBB1	METAP1	CadherinE	0.915	0.795	1.711	0.904
		HSP90b	SCFsR	CK-MB	YES				
42	RGM-C	C9	ERBB1	CadherinE	METAP1	0.906	0.807	1.713	0.912
		SCFsR	CK-MB	NAGK	IGFBP-2				
43	VEGF	RGM-C	ERBB1	METAP1	CK-MB	0.911	0.781	1.692	0.895
		CadherinE	CalpainI	SCFsR	CATC				
44	RGM-C	METAP1	SCFsR	ERBB1	YES	0.897	0.814	1.711	0.905
		CadherinE	CK-MB	b-ECGF	CD30Ligand				
45	IMB1	HSP90a	ERBB1	CadherinE	RGM-C	0.887	0.798	1.685	0.893
		SCFsR	IGFBP-2	CK-MB	Cadherin-6				
46	CSK	KPCI	ERBB1	CadherinE	CK-MB	0.911	0.795	1.706	0.899
		YES	MMR	RGM-C	Catalase				
47	RGM-C	MMP-7	HSP90b	METAP1	CadherinE	0.897	0.814	1.711	0.903
		SCFsR	ERBB1	HMG-1	CK-MB				
48	CNDP1	ERBB1	CadherinE	METAP1	CK-MB	0.911	0.8	1.711	0.893
		YES	NACA	IL-17B	SCFsR				
49	SCFsR	ERBB1	CadherinE	CalpainI	RGM-C	0.878	0.814	1.692	0.891
		HSP90a	b-ECGF	IGFBP-2	LGMN				
50	YES	CadherinE	ERBB1	RGM-C	CSK	0.892	0.817	1.709	0.912
		CK-MB	LRIG3	GAPDH, liver	MMR				
51	CK-MB	SCFsR	METAP1	CadherinE	ERBB1	0.906	0.807	1.713	0.907
		IGFBP-2	RGM-C	CalpainI	MEK1				
52	RGM-C	CK-MB	ERBB1	IMB1	CadherinE	0.901	0.807	1.709	0.901
		YES	SCFsR	MMR	MK13				
53	RGM-C	FGF-17	ERBB1	CalpainI	CadherinE	0.883	0.821	1.704	0.898
		CK-MB	SCFsR	NAGK	Proteinase-3				
54	NACA	CadherinE	ERBB1	METAP1	CK-MB	0.906	0.805	1.711	0.9
		MMR	RGM-C	Prothrombin	IGFBP-2				
55	CK-MB	MMP-7	METAP1	RGM-C	ERBB1	0.901	0.807	1.709	0.912
		CadherinE	HSP90a	ApoA-I	SCFsR				
56	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.883	0.817	1.699	0.9
		CadherinE	BLC	CK-MB	MMP-7				
57	RGM-C	BMP-1	ERBB1	METAP1	CadherinE	0.911	0.798	1.708	0.894
		HSP90b	SCFsR	GAPDH, liver	YES				
58	CSK	CadherinE	MMP-7	KPCI	SCFsR	0.911	0.8	1.711	0.898
		RGM-C	CK-MB	C9	GAPDH, liver				
59	b-ECGF	CadherinE	ERBB1	METAP1	RGM-C	0.911	0.781	1.692	0.893
		CK-MB	HSP90b	SCFsR	CATC				
60	MMR	ERBB1	METAP1	CK-MB	CadherinE	0.901	0.81	1.711	0.907
		YES	RGM-C	IGFBP-2	CD30Ligand				
61	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	0.887	0.793	1.68	0.89
		METAP1	MMR	SCFsR	Cadherin-6				
62	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	0.915	0.79	1.706	0.896
		SCFsR	MMR	RGM-C	Catalase				
63	CathepsinH	CSK	ERBB1	RGM-C	CadherinE	0.911	0.8	1.711	0.899
		YES	SCFsR	KPCI	CNDP1				
64	MMR	SCFsR	CadherinE	CalpainI	ERBB1	0.892	0.817	1.709	0.906
		RGM-C	CK-MB	HMG-1	YES				
65	SCFsR	NAGK	CadherinE	CK-MB	RGM-C	0.901	0.807	1.709	0.89
		ERBB1	IL-17B	KPCI	CalpainI				
66	YES	CadherinE	ERBB1	CSK	SCFsR	0.892	0.8	1.692	0.894
		CK-MB	MMP-7	KPCI	LGMN				
67	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	0.901	0.807	1.709	0.901
		RGM-C	CK-MB	CSK	LRIG3				
68	YES	CadherinE	ERBB1	CSK	SCFsR	0.887	0.824	1.711	0.908
		CK-MB	MMP-7	GAPDH, liver	MEK1				
69	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	0.901	0.805	1.706	0.902
		METAP1	MMR	SCFsR	MK13				
70	YES	CadherinE	ERBB1	CSK	SCFsR	0.906	0.798	1.704	0.896
		RGM-C	MMP-7	KPCI	Proteinase-3				

TABLE 8-continued

71	CK-MB	MMP-7	METAP1	RGM-C	SCFsR	0.92	0.79	1.711	0.903
		CadherinE	b-ECGF	HSP90a	Prothrombin				
72	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.92	0.793	1.713	0.896
		RGM-C	ERBB1	VEGF	YES				
73	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.901	0.807	1.709	0.909
		CadherinE	VEGF	CK-MB	ApoA-I				
74	CK-MB	MMP-7	METAP1	RGM-C	CadherinE	0.873	0.824	1.697	0.898
		MK13	ERBB1	IGFBP-2	BLC				
75	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	0.887	0.819	1.706	0.906
		VEGF	CSK	MMP-7	BMP-1				
76	CK-MB	MMP-7	METAP1	RGM-C	CadherinE	0.892	0.817	1.709	0.913
		NAGK	SCFsR	C9	ERBB1				
77	CD30Ligand	METAP1	CK-MB	ERBB1	CadherinE	0.892	0.798	1.69	0.887
		YES	NAGK	RGM-C	CATC				
78	RGM-C	KPCI	SCFsR	BMP-1	CadherinE	0.873	0.805	1.678	0.889
		CK-MB	ERBB1	CSK	Cadherin-6				
79	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	0.897	0.807	1.704	0.894
		YES	METAP1	CK-MB	Catalase				
80	CathepsinH	RGM-C	METAP1	CK-MB	CadherinE	0.887	0.821	1.709	0.909
		ERBB1	SCFsR	YES	MMP-7				
81	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	0.915	0.81	1.725	0.912
		CK-MB	METAP1	SCFsR	FGF-17				
82	HSP90b	KPCI	ERBB1	CadherinE	RGM-C	0.892	0.817	1.709	0.888
		SCFsR	MMR	CSK	HMG-1				
83	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.906	0.802	1.708	0.89
		RGM-C	ERBB1	IL-17B	HSP90b				
84	RGM-C	CadherinE	HSP90a	CK-MB	YES	0.911	0.8	1.711	0.896
		ERBB1	SCFsR	IMB1	METAP1				
85	RGM-C	CK-MB	ERBB1	IMB1	CadherinE	0.883	0.805	1.687	0.895
		SCFsR	CNDP1	HSP90a	LGMN				
86	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	0.906	0.802	1.708	0.893
		SCFsR	MMR	LRIG3	YES				
87	METAP1	GAPDH, liver	MMP-7	CadherinE	ERBB1	0.897	0.812	1.709	0.912
		CK-MB	RGM-C	MEK1	SCFsR				
88	YES	CadherinE	KPCI	CK-MB	ERBB1	0.887	0.814	1.702	0.897
		CNDP1	Proteinase-3	SCFsR	Catalase				
89	Prothrombin	CadherinE	ERBB1	METAP1	YES	0.906	0.802	1.708	0.896
		MMP-7	CK-MB	SCFsR	KPCI				
90	RGM-C	METAP1	SCFsR	ERBB1	YES	0.92	0.788	1.708	0.906
		CadherinE	MMP-7	ApoA-I	HSP90a				
91	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	0.887	0.81	1.697	0.904
		MMP-7	RGM-C	CSK	BLC				
92	SCFsR	ERBB1	CadherinE	IMB1	CSK	0.901	0.807	1.709	0.903
		CNDP1	CK-MB	YES	C9				
93	CK-MB	ERBB1	CadherinE	NAGK	CSK	0.892	0.798	1.69	0.895
		SCFsR	RGM-C	YES	CATC				
94	CD30Ligand	KPCI	ERBB1	SCFsR	CadherinE	0.901	0.81	1.711	0.898
		CK-MB	CSK	YES	CNDP1				
95	YES	CadherinE	KPCI	CK-MB	ERBB1	0.892	0.786	1.678	0.885
		METAP1	MMP-7	CNDP1	Cadherin-6				
96	RGM-C	METAP1	SCFsR	ERBB1	YES	0.901	0.807	1.709	0.909
		CadherinE	MMR	CathepsinH	CK-MB				
97	CK-MB	MMP-7	METAP1	RGM-C	CadherinE	0.906	0.814	1.72	0.91
		NAGK	SCFsR	FGF-17	ERBB1				
98	RGM-C	CadherinE	KPCI	MMP-7	ERBB1	0.892	0.812	1.704	0.895
		CK-MB	NAGK	SCFsR	HMG-1				
99	HSP90b	GAPDH, liver	ERBB1	CadherinE	RGM-C	0.892	0.814	1.706	0.898
		IL-17B	SCFsR	CK-MB	YES				
100	YES	CadherinE	KPCI	CK-MB	SCFsR	0.883	0.805	1.687	0.892
		ERBB1	HSP90a	CNDP1	LGMN				

Marker	Count	Marker	Count
CadherinE	100	VEGF	6
ERBB1	93	LGMN	6
RGM-C	86	IL-17B	6
CK-MB	86	HMG-1	6
SCFsR	82	FGF-17	6
YES	56	CathepsinH	6
METAP1	55	Catalase	6
MMP-7	36	Cadherin-6	6
CSK	30	CD30Ligand	6
KPCI	29	CATC	6
MMR	21	C9	6
GAPDH, liver	19	BMP-1	6
IGFBP-2	14	BLC	6
HSP90a	14	ApoA-I	6
NAGK	13	Prothrombin	5
HSP90b	13	Proteinase-3	5
CNDP1	12	NACA	5

TABLE 8-continued

CalpainI	11	MK13	5
b-ECGF	9	MEK1	5
IMB1	7	LRIG3	5

TABLE 9

100 Panels of 10 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers					Sensitivity	Specificity	Sens. + Spec.	AUC
1	b-ECGF	CadherinE	ERBB1	METAP1	RGM-C	0.915	0.819	1.735	0.912
	CK-MB	MMP-7	SCFsR	ApoA-I	YES				
2	CK-MB	SCFsR	METAP1	CadherinE	ERBB1	0.883	0.829	1.711	0.896
	IGFBP-2	RGM-C	CD30Ligand	MK13	BLC				
3	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	0.915	0.807	1.723	0.904
	YES	METAP1	SCFsR	CK-MB	BMP-1				
4	CD30Ligand	METAP1	CK-MB	ERBB1	CadherinE	0.911	0.812	1.723	0.907
	YES	NAGK	RGM-C	SCFsR	C9				
5	YES	CadherinE	ERBB1	CSK	SCFsR	0.901	0.807	1.709	0.905
	RGM-C	MMP-7	GAPDH, liver	CK-MB	CATC				
6	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	0.911	0.819	1.73	0.904
	METAP1	MMR	SCFsR	MK13	CNDP1				
7	SCFsR	ERBB1	CadherinE	CalpainI	RGM-C	0.873	0.819	1.692	0.894
	HSP90a	b-ECGF	CK-MB	C9	Cadherin-6				
8	CSK	KPCI	ERBB1	CadherinE	CK-MB	0.911	0.807	1.718	0.9
	YES	MMR	RGM-C	Catalase	ApoA-I				
9	CK-MB	MMP-7	METAP1	RGM-C	CadherinE	0.897	0.824	1.721	0.907
	MK13	ERBB1	SCFsR	IGFBP-2	CathepsinH				
10	METAP1	GAPDH, liver	MMP-7	CadherinE	ERBB1	0.934	0.812	1.746	0.912
	YES	CK-MB	SCFsR	FGF-17	RGM-C				
11	b-ECGF	CadherinE	ERBB1	METAP1	RGM-C	0.911	0.81	1.72	0.903
	CK-MB	HSP90b	SCFsR	MMR	HMG-1				
12	CadherinE	METAP1	CK-MB	HSP90b	ERBB1	0.92	0.807	1.727	0.901
	YES	SCFsR	RGM-C	IGFBP-2	IL-17B				
13	CK-MB	CNDP1	IMB1	CadherinE	ERBB1	0.92	0.805	1.725	0.9
	YES	METAP1	SCFsR	HSP90a	RGM-C				
14	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	0.892	0.812	1.704	0.892
	RGM-C	CK-MB	CalpainI	LRIG3	LGMN				
15	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.906	0.821	1.728	0.912
	MMR	YES	RGM-C	MEK1	SCFsR				
16	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.92	0.802	1.723	0.895
	CadherinE	b-ECGF	NACA	CK-MB	YES				
17	RGM-C	CK-MB	ERBB1	CSK	CadherinE	0.901	0.812	1.713	0.901
	CNDP1	YES	SCFsR	KPCI	Proteinase-3				
18	CK-MB	MMP-7	METAP1	RGM-C	SCFsR	0.92	0.807	1.727	0.911
	CadherinE	b-ECGF	YES	Prothrombin	ERBB1				
19	VEGF	METAP1	ERBB1	YES	CadherinE	0.925	0.793	1.718	0.896
	CK-MB	NACA	HSP90a	SCFsR	RGM-C				
20	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	0.897	0.814	1.711	0.901
	CK-MB	CSK	MEK1	YES	BLC				
21	MMR	ERBB1	METAP1	CK-MB	CadherinE	0.906	0.812	1.718	0.912
	YES	RGM-C	GAPDH, liver	BMP-1	IGFBP-2				
22	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.901	0.8	1.701	0.902
	YES	BMP-1	SCFsR	RGM-C	CATC				
23	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	0.897	0.793	1.69	0.891
	METAP1	MMR	SCFsR	MK13	Cadherin-6				
24	RGM-C	C9	ERBB1	CadherinE	METAP1	0.901	0.814	1.716	0.911
	SCFsR	CK-MB	NAGK	IGFBP-2	Catalase				
25	CadherinE	METAP1	CK-MB	HSP90b	ERBB1	0.915	0.8	1.715	0.898
	YES	SCFsR	RGM-C	HSP90a	CathepsinH				
26	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	0.906	0.824	1.73	0.914
	CK-MB	CSK	MMR	FGF-17	YES				
27	RGM-C	METAP1	SCFsR	ERBB1	YES	0.901	0.814	1.716	0.9
	CadherinE	CK-MB	BMP-1	HMG-1	HSP90b				
28	SCFsR	NAGK	CadherinE	CK-MB	RGM-C	0.911	0.812	1.723	0.897
	ERBB1	IL-17B	METAP1	MMP-7	KPCI				
29	CK-MB	SCFsR	METAP1	CadherinE	ERBB1	0.93	0.793	1.722	0.9
	IGFBP-2	YES	RGM-C	IMB1	IL-17B				
30	CSK	CalpainI	ERBB1	RGM-C	CadherinE	0.887	0.812	1.699	0.9
	MMP-7	CK-MB	BMP-1	YES	LGMN				
31	MMR	ERBB1	METAP1	CK-MB	CadherinE	0.911	0.807	1.718	0.91
	YES	LRIG3	RGM-C	IGFBP-2	GAPDH, liver				
32	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.911	0.8	1.711	0.9
	RGM-C	ERBB1	Proteinase-3	CK-MB	YES				
33	RGM-C	CadherinE	KPCI	CK-MB	HSP90a	0.915	0.805	1.72	0.896
	IGFBP-2	SCFsR	ERBB1	Prothrombin	METAP1				

TABLE 9-continued

34	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	0.901	0.814	1.716	0.906
	CSK	VEGF	YES	CNDP1	BMP-1				
35	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.915	0.802	1.718	0.912
	CadherinE	CK-MB	ApoA-I	YES	MMP-7				
36	YES	CadherinE	ERBB1	CSK	SCFsR	0.906	0.805	1.711	0.897
	CK-MB	MMP-7	KPCI	RGM-C	BLC				
37	RGM-C	CK-MB	ERBB1	CSK	CadherinE	0.901	0.8	1.701	0.903
	CNDP1	YES	SCFsR	GAPDH, liver	CATC				
38	RGM-C	CK-MB	ERBB1	CSK	CadherinE	0.92	0.805	1.725	0.902
	CNDP1	YES	SCFsR	KPCI	CD30Ligand				
39	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.878	0.81	1.687	0.898
	YES	MMP-7	C9	RGM-C	Cadherin-6				
40	YES	CadherinE	ERBB1	CSK	SCFsR	0.915	0.8	1.715	0.901
	CK-MB	MMP-7	KPCI	CNDP1	Catalase				
41	RGM-C	KPCI	SCFsR	ERBB1	Catalase	0.911	0.802	1.713	0.9
	CK-MB	CadherinE	METAP1	IGFBP-2	CathepsinH				
42	MMR	ERBB1	METAP1	CK-MB	CadherinE	0.925	0.805	1.73	0.91
	YES	RGM-C	GAPDH, liver	FGF-17	SCFsR				
43	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.906	0.81	1.716	0.899
	CK-MB	YES	ERBB1	HMG-1	RGM-C				
44	SCFsR	ERBB1	CadherinE	METAP1	IMB1	0.93	0.788	1.718	0.902
	RGM-C	MMP-7	CK-MB	IL-17B	YES				
45	YES	CadherinE	ERBB1	CSK	SCFsR	0.897	0.802	1.699	0.891
	RGM-C	MMP-7	GAPDH, liver	KPCI	LGMN				
46	RGM-C	METAP1	SCFsR	ERBB1	YES	0.915	0.802	1.718	0.907
	CadherinE	MMP-7	CK-MB	LRIG3	HSP90b				
47	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	0.906	0.819	1.725	0.914
	CK-MB	CSK	MEK1	YES	MMP-7				
48	RGM-C	CK-MB	ERBB1	CSK	CadherinE	0.915	0.802	1.718	0.902
	CNDP1	YES	SCFsR	HSP90a	NACA				
49	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	0.887	0.821	1.709	0.908
	CNDP1	CK-MB	Prothrombin	YES	Proteinase-3				
50	VEGF	RGM-C	ERBB1	METAP1	CK-MB	0.92	0.795	1.715	0.915
	CadherinE	MMR	GAPDH, liver	SCFsR	C9				
51	CK-MB	MMP-7	METAP1	RGM-C	SCFsR	0.925	0.793	1.718	0.906
	CadherinE	b-ECGF	HSP90a	ApoA-I	Prothrombin				
52	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.915	0.795	1.711	0.892
	CadherinE	IGFBP-2	KPCI	CK-MB	BLC				
53	METAP1	GAPDH, liver	MMP-7	CadherinE	ERBB1	0.911	0.79	1.701	0.905
	YES	CK-MB	SCFsR	RGM-C	CATC				
54	RGM-C	METAP1	SCFsR	ERBB1	YES	0.925	0.795	1.72	0.901
	CadherinE	CD30Ligand	CK-MB	MMR	KPCI				
55	SCFsR	ERBB1	CadherinE	IMB1	CSK	0.883	0.805	1.687	0.895
	CNDP1	CK-MB	b-ECGF	RGM-C	Cadherin-6				
56	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.915	0.805	1.72	0.896
	CadherinE	CalpainI	CK-MB	b-ECGF	NAGK				
57	METAP1	HSP90a	CadherinE	ERBB1	CK-MB	0.911	0.802	1.713	0.902
	SCFsR	YES	NAGK	RGM-C	CathepsinH				
58	FGF-17	CadherinE	ERBB1	HSP90b	SCFsR	0.906	0.817	1.723	0.904
	RGM-C	METAP1	CK-MB	IGFBP-2	YES				
59	YES	CadherinE	MMP-7	HMG-1	ERBB1	0.892	0.821	1.713	0.907
	CK-MB	RGM-C	SCFsR	Prothrombin	HSP90b				
60	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	0.906	0.793	1.699	0.895
	RGM-C	CSK	MMP-7	YES	LGMN				
61	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	0.901	0.814	1.716	0.912
	LRIG3	MMR	CSK	IGFBP-2	RGM-C				
62	CadherinE	METAP1	CK-MB	HSP90b	ERBB1	0.906	0.812	1.718	0.904
	YES	SCFsR	RGM-C	IGFBP-2	MEK1				
63	MMP-7	ERBB1	YES	METAP1	CadherinE	0.915	0.802	1.718	0.9
	NACA	CK-MB	SCFsR	CNDP1	FGF-17				
64	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	0.901	0.807	1.709	0.907
	CK-MB	METAP1	SCFsR	FGF-17	Proteinase-3				
65	METAP1	HSP90a	CadherinE	ERBB1	CK-MB	0.92	0.795	1.715	0.903
	SCFsR	YES	NAGK	RGM-C	VEGF				
66	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	0.901	0.814	1.716	0.916
	MMP-7	RGM-C	CSK	ApoA-I	SCFsR				
67	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	0.878	0.831	1.709	0.906
	CK-MB	CSK	MMR	IGFBP-2	BLC				
68	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.906	0.79	1.697	0.894
	CK-MB	YES	ERBB1	RGM-C	CATC				
69	RGM-C	METAP1	SCFsR	ERBB1	YES	0.925	0.795	1.72	0.911
	CadherinE	CD30Ligand	CK-MB	MMR	GAPDH, liver				
70	LRIG3	CadherinE	ERBB1	CalpainI	RGM-C	0.878	0.807	1.685	0.893
	CK-MB	SCFsR	YES	CD30Ligand	Cadherin-6				
71	RGM-C	KPCI	SCFsR	ERBB1	Catalase	0.906	0.807	1.713	0.903
	CK-MB	CadherinE	METAP1	IGFBP-2	CNDP1				
72	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.901	0.81	1.711	0.912
	MMR	YES	RGM-C	CathepsinH	SCFsR				
73	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.901	0.812	1.713	0.897
	RGM-C	ERBB1	IL-17B	CK-MB	HMG-1				

TABLE 9-continued

74	CadherinE	MK13	MMR	IMB1	ERBB1	0.906	0.81	1.716	0.908
	RGM-C	SCFsR	METAP1	CNDP1	CK-MB				
75	YES	CadherinE	ERBB1	CSK	SCFsR	0.883	0.814	1.697	0.907
	RGM-C	MMP-7	GAPDH, liver	CK-MB	LGMN				
76	SCFsR	ERBB1	CadherinE	METAP1	RGM-C	0.911	0.805	1.716	0.9
	NAGK	CK-MB	CalpainI	MEK1	b-ECGF				
77	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.92	0.798	1.718	0.899
	CadherinE	b-ECGF	NACA	CK-MB	IGFBP-2				
78	RGM-C	METAP1	SCFsR	ERBB1	YES	0.925	0.783	1.708	0.898
	CadherinE	CK-MB	CNDP1	NACA	Proteinase-3				
79	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.925	0.79	1.715	0.894
	CadherinE	YES	NACA	BMP-1	VEGF				
80	MMR	CSK	CadherinE	CK-MB	RGM-C	0.901	0.814	1.716	0.917
	ERBB1	GAPDH, liver	ApoA-I	YES	IGFBP-2				
81	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	0.883	0.824	1.706	0.905
	MMP-7	RGM-C	CSK	BLC	SCFsR				
82	RGM-C	C9	ERBB1	CadherinE	METAP1	0.915	0.805	1.72	0.912
	YES	CK-MB	MMP-7	NAGK	SCFsR				
83	YES	METAP1	MMP-7	CadherinE	RGM-C	0.911	0.786	1.697	0.902
	ERBB1	CK-MB	Prothrombin	SCFsR	CATC				
84	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	0.892	0.793	1.685	0.9
	CK-MB	METAP1	C9	SCFsR	Cadherin-6				
85	CSK	SCFsR	CadherinE	C9	ERBB1	0.906	0.807	1.713	0.903
	IGFBP-2	CK-MB	KPCI	CNDP1	Catalase				
86	SCFsR	MMP-7	CadherinE	KPCI	METAP1	0.906	0.805	1.711	0.897
	RGM-C	ERBB1	IL-17B	CK-MB	CathepsinH				
87	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.892	0.819	1.711	0.911
	MMR	YES	RGM-C	HMG-1	SCFsR				
88	METAP1	HSP90b	CadherinE	ERBB1	RGM-C	0.911	0.805	1.716	0.896
	IL-17B	CK-MB	SCFsR	IGFBP-2	IMB1				
89	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	0.892	0.805	1.697	0.895
	RGM-C	YES	HSP90a	CK-MB	LGMN				
90	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.906	0.81	1.716	0.908
	CadherinE	CK-MB	ApoA-I	YES	LRIG3				
91	METAP1	GAPDH, liver	MMP-7	CadherinE	ERBB1	0.915	0.8	1.715	0.912
	YES	CK-MB	SCFsR	MEK1	RGM-C				
92	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.911	0.812	1.723	0.898
	CadherinE	IGFBP-2	KPCI	CK-MB	MK13				
93	YES	CadherinE	KPCI	CK-MB	ERBB1	0.897	0.81	1.706	0.894
	CNDP1	Proteinase-3	SCFsR	Catalase	b-ECGF				
94	RGM-C	CK-MB	ERBB1	CSK	CadherinE	0.897	0.817	1.713	0.911
	CD30Ligand	YES	SCFsR	GAPDH, liver	VEGF				
95	CK-MB	SCFsR	METAP1	CadherinE	MMP-7	0.906	0.8	1.706	0.904
	GAPDH, liver	RGM-C	ERBB1	BLC	FGF-17				
96	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	0.901	0.793	1.694	0.9
	YES	MMP-7	C9	RGM-C	CATC				
97	RGM-C	CadherinE	KPCI	CK-MB	HSP90a	0.883	0.8	1.683	0.892
	IGFBP-2	SCFsR	ERBB1	Prothrombin	Cadherin-6				
98	SCFsR	ERBB1	CadherinE	CalpainI	RGM-C	0.911	0.807	1.718	0.895
	HSP90a	KPCI	Prothrombin	CK-MB	MMR				
99	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	0.906	0.805	1.711	0.897
	CadherinE	IGFBP-2	KPCI	CK-MB	CathepsinH				
100	HMG-1	CalpainI	ERBB1	CadherinE	CK-MB	0.901	0.81	1.711	0.906
	RGM-C	MMP-7	SCFsR	b-ECGF	CSK				

Marker	Count	Marker	Count
CadherinE	100	CalpainI	8
ERBB1	99	NACA	7
RGM-C	96	IL-17B	7
CK-MB	96	HMG-1	7
SCFsR	91	FGF-17	7
YES	67	CathepsinH	7
METAP1	60	Catalase	7
MMP-7	34	Cadherin-6	7
GAPDH, liver	32	CD30Ligand	7
CSK	31	CATC	7
KPCI	28	BMP-1	7
MMR	22	BLC	7
IGFBP-2	22	ApoA-I	7
HSP90a	21	VEGF	6
CNDP1	19	Proteinase-3	6
b-ECGF	13	MK13	6
HSP90b	10	MEK1	6
C9	9	LRIG3	6
Prothrombin	8	LGMN	6
NAGK	8	IMB1	6

TABLE 10

100 Panels of 11 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers						Sensitivity	Specificity	Sens. + Spec.	AUC
1	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.925	0.8	1.725	0.911
		CK-MB	Catalase	MMP-7	b-ECGF	ApoA-I				
2	CD30Ligand	METAP1	CK-MB	ERBB1	CadherinE	YES	0.901	0.812	1.713	0.896
		RGM-C	IGFBP-2	SCFsR	b-ECGF	BLC				
3	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.92	0.812	1.732	0.911
		CK-MB	CNDP1	GAPDH, liver	b-ECGF	BMP-1				
4	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	MMR	0.897	0.826	1.723	0.912
		YES	RGM-C	C9	SCFsR	MEK1				
5	MMR	CSK	CadherinE	CK-MB	RGM-C	ERBB1	0.92	0.802	1.723	0.904
		GAPDH, liver	ApoA-I	YES	IGFBP-2	CATC				
6	CK-MB	GAPDH, liver	ERBB1	HSP90a	CadherinE	YES	0.878	0.817	1.695	0.902
		SCFsR	CNDP1	RGM-C	IGFBP-2	Cadherin-6				
7	b-ECGF	CadherinE	ERBB1	METAP1	RGM-C	CK-MB	0.915	0.81	1.725	0.905
		MMP-7	SCFsR	NAGK	CalpainI	FGF-17				
8	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.911	0.812	1.723	0.901
		CK-MB	BMP-1	HMG-1	HSP90b	CathepsinH				
9	CNDP1	ERBB1	CadherinE	METAP1	CK-MB	YES	0.934	0.795	1.73	0.901
		NACA	IL-17B	IGFBP-2	RGM-C	SCFsR				
10	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	0.92	0.807	1.727	0.9
		CNDP1	CK-MB	HSP90a	b-ECGF	YES				
11	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.93	0.805	1.734	0.903
		CK-MB	CNDP1	KPCI	IGFBP-2	CD30Ligand				
12	YES	CadherinE	KPCI	CK-MB	SCFsR	ERBB1	0.915	0.79	1.706	0.891
		HSP90a	CNDP1	METAP1	RGM-C	LGMN				
13	CadherinE	METAP1	CK-MB	HSP90b	ERBB1	YES	0.92	0.805	1.725	0.905
		SCFsR	RGM-C	MMR	LRIG3	MK13				
14	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.925	0.795	1.72	0.901
		CK-MB	NACA	CNDP1	b-ECGF	Proteinase-3				
15	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	MMP-7	0.915	0.81	1.725	0.915
		RGM-C	CSK	MEK1	Prothrombin	SCFsR				
16	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	VEGF	0.911	0.819	1.73	0.913
		RGM-C	CSK	BMP-1	MMR	SCFsR				
17	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.892	0.819	1.711	0.9
		CK-MB	MMR	GAPDH, liver	BLC	MEK1				
18	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	0.901	0.821	1.723	0.913
		CSK	MMR	FGF-17	C9	YES				
19	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	0.911	0.8	1.711	0.897
		RGM-C	GAPDH, liver	FGF-17	IGFBP-2	CATC				
20	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.887	0.807	1.694	0.896
		YES	SCFsR	KPCI	MMR	Cadherin-6				
21	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	0.915	0.81	1.725	0.897
		IL-17B	SCFsR	IGFBP-2	CalpainI	CNDP1				
22	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	0.925	0.8	1.725	0.904
		MMR	SCFsR	YES	Catalase	IGFBP-2				
23	CadherinE	METAP1	CK-MB	HSP90b	ERBB1	YES	0.925	0.798	1.723	0.904
		SCFsR	RGM-C	MMR	LRIG3	CathepsinH				
24	CD30Ligand	METAP1	CK-MB	ERBB1	CadherinE	YES	0.915	0.812	1.727	0.897
		RGM-C	IGFBP-2	SCFsR	KPCI	HMG-1				
25	CK-MB	CNDP1	IMB1	CadherinE	ERBB1	YES	0.925	0.802	1.727	0.901
		METAP1	SCFsR	HSP90a	VEGF	RGM-C				
26	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C	0.892	0.812	1.704	0.89
		CK-MB	CalpainI	CD30Ligand	b-ECGF	LGMN				
27	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.925	0.807	1.732	0.904
		CK-MB	CNDP1	KPCI	MMR	MK13				
28	YES	CadherinE	ERBB1	RGM-C	NAGK	CalpainI	0.925	0.8	1.725	0.896
		SCFsR	CK-MB	IL-17B	METAP1	b-ECGF				
29	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	VEGF	0.897	0.819	1.716	0.908
		RGM-C	CSK	CNDP1	SCFsR	Proteinase-3				
30	YES	CadherinE	ERBB1	CSK	SCFsR	CK-MB	0.901	0.821	1.723	0.914
		MMP-7	GAPDH, liver	Prothrombin	RGM-C	FGF-17				
31	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.892	0.831	1.723	0.913
		MMP-7	GAPDH, liver	MEK1	ApoA-I	CK-MB				
32	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	0.901	0.81	1.711	0.907
		METAP1	C9	SCFsR	IGFBP-2	BLC				
33	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.906	0.802	1.708	0.906
		IGFBP-2	CK-MB	GAPDH, liver	MMP-7	CATC				
34	RGM-C	C9	ERBB1	CadherinE	METAP1	SCFsR	0.892	0.8	1.692	0.895
		CK-MB	NAGK	IGFBP-2	Catalase	Cadherin-6				
35	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	0.901	0.819	1.72	0.908
		CSK	MEK1	YES	BMP-1	CathepsinH				
36	RGM-C	BMP-1	ERBB1	METAP1	CadherinE	HSP90b	0.906	0.814	1.72	0.902
		SCFsR	CK-MB	YES	VEGF	HMG-1				
37	SCFsR	ERBB1	CadherinE	IMB1	CSK	CNDP1	0.925	0.802	1.727	0.905
		CK-MB	b-ECGF	RGM-C	YES	VEGF				

TABLE 10-continued

38	CK-MB	GAPDH, liver SCFsR	ERBB1 CNDP1	HSP90a RGM-C	CadherinE IGFBP-2	YES LGMN	0.878	0.824	1.702	0.905
39	YES	CK-MB MMR	ERBB1 CSK	CadherinE IGFBP-2	GAPDH, liver RGM-C	LRIG3 SCFsR	0.901	0.821	1.723	0.914
40	MMR	ERBB1 RGM-C	METAP1 IGFBP-2	CK-MB MK13	CadherinE SCFsR	YES KPCI	0.925	0.805	1.73	0.903
41	YES	CK-MB IGFBP-2	ERBB1 RGM-C	CadherinE SCFsR	METAP1 NACA	MMP-7 HSP90a	0.934	0.798	1.732	0.903
42	METAP1	GAPDH, liver CK-MB	MMP-7 SCFsR	CadherinE MEK1	ERBB1 RGM-C	YES Proteinase-3	0.901	0.814	1.716	0.907
43	RGM-C	CK-MB YES	ERBB1 GAPDH, liver	CSK MMR	CadherinE VEGF	CNDP1 Prothrombin	0.906	0.817	1.723	0.911
44	CK-MB	IGFBP-2 YES	CSK FGF-17	CadherinE GAPDH, liver	RGM-C MMR	ERBB1 ApoA-I	0.901	0.821	1.723	0.914
45	RGM-C	CadherinE CSK	ERBB1 MMR	GAPDH, liver IGFBP-2	SCFsR BLC	CK-MB ApoA-I	0.883	0.826	1.709	0.908
46	YES	CK-MB IGFBP-2	ERBB1 RGM-C	CadherinE SCFsR	METAP1 GAPDH, liver	MMP-7 CATC	0.915	0.793	1.708	0.906
47	CNDP1	ERBB1 CK-MB	CadherinE CalpainI	KPCI CD30Ligand	SCFsR b-ECGF	RGM-C Cadherin-6	0.878	0.812	1.69	0.89
48	CNDP1	ERBB1 CK-MB	CadherinE CalpainI	KPCI Catalase	SCFsR IGFBP-2	RGM-C CSK	0.906	0.817	1.723	0.902
49	MMR	ERBB1 HSP90b	GAPDH, liver SCFsR	CadherinE YES	RGM-C LRIG3	CK-MB CathepsinH	0.911	0.81	1.72	0.902
50	CSK	CadherinE YES	CK-MB RGM-C	GAPDH, liver HMG-1	ERBB1 SCFsR	MMR FGF-17	0.887	0.831	1.718	0.91
51	RGM-C	METAP1 CK-MB	SCFsR CNDP1	ERBB1 KPCI	YES IGFBP-2	CadherinE IL-17B	0.93	0.798	1.727	0.901
52	SCFsR	ERBB1 CK-MB	HSP90a GAPDH, liver	YES RGM-C	CadherinE CNDP1	IMB1 b-ECGF	0.915	0.81	1.725	0.9
53	METAP1	GAPDH, liver CK-MB	MMP-7 SCFsR	CadherinE MEK1	ERBB1 RGM-C	YES LGMN	0.901	0.8	1.701	0.903
54	YES	CadherinE MMR	ERBB1 CK-MB	RGM-C SCFsR	METAP1 MK13	NACA IGFBP-2	0.93	0.793	1.722	0.903
55	RGM-C	METAP1 NAGK	SCFsR MMP-7	ERBB1 CK-MB	YES Catalase	CadherinE ApoA-I	0.911	0.81	1.72	0.91
56	CD30Ligand	METAP1 RGM-C	CK-MB IGFBP-2	ERBB1 SCFsR	CadherinE KPCI	YES Proteinase-3	0.92	0.795	1.715	0.898
57	CSK	KPCI YES	ERBB1 SCFsR	CadherinE ApoA-I	RGM-C CNDP1	MMR Prothrombin	0.915	0.807	1.723	0.901
58	CSK	CadherinE IGFBP-2	CK-MB RGM-C	GAPDH, liver CD30Ligand	ERBB1 SCFsR	YES BLC	0.892	0.817	1.709	0.903
59	CSK	CadherinE YES	CK-MB RGM-C	GAPDH, liver C9	ERBB1 SCFsR	MMR LRIG3	0.906	0.817	1.723	0.913
60	FGF-17	CadherinE METAP1	ERBB1 CK-MB	HSP90b IGFBP-2	SCFsR YES	RGM-C CATC	0.915	0.79	1.706	0.894
61	CNDP1	CalpainI SCFsR	ERBB1 IMB1	CadherinE b-ECGF	RGM-C IL-17B	CK-MB Cadherin-6	0.883	0.807	1.69	0.89
62	RGM-C	METAP1 CalpainI	SCFsR CK-MB	ERBB1 b-ECGF	HSP90a NAGK	CadherinE CathepsinH	0.915	0.805	1.72	0.896
63	MMR	CSK GAPDH, liver	CadherinE ApoA-I	CK-MB YES	RGM-C IGFBP-2	ERBB1 HMG-1	0.897	0.821	1.718	0.912
64	CK-MB	SCFsR RGM-C	METAP1 ERBB1	CadherinE HSP90a	MMP-7 YES	GAPDH, liver LGMN	0.911	0.79	1.701	0.9
65	CNDP1	ERBB1 YES	CadherinE HSP90a	KPCI CK-MB	SCFsR IMB1	RGM-C MK13	0.906	0.814	1.72	0.894
66	CK-MB	SCFsR YES	METAP1 RGM-C	CadherinE HSP90a	ERBB1 CNDP1	IGFBP-2 NACA	0.93	0.798	1.727	0.902
67	YES	CadherinE CK-MB	ERBB1 MMR	CSK GAPDH, liver	SCFsR Proteinase-3	RGM-C IGFBP-2	0.892	0.821	1.713	0.912
68	YES	CadherinE CK-MB	ERBB1 VEGF	CSK GAPDH, liver	SCFsR Prothrombin	RGM-C MMR	0.92	0.802	1.723	0.914
69	CK-MB	SCFsR RGM-C	METAP1 ERBB1	CadherinE BLC	MMP-7 FGF-17	GAPDH, liver NAGK	0.897	0.812	1.709	0.902
70	CSK	CadherinE BMP-1	CK-MB SCFsR	GAPDH, liver RGM-C	ERBB1 CNDP1	YES VEGF	0.906	0.821	1.728	0.914
71	YES	CadherinE RGM-C	GAPDH, liver CSK	MMP-7 LRIG3	SCFsR CNDP1	CK-MB C9	0.911	0.812	1.723	0.91
72	MMR	ERBB1 SCFsR	METAP1 KPCI	CK-MB IGFBP-2	CadherinE RGM-C	YES CATC	0.92	0.786	1.706	0.895
73	YES	CadherinE IGFBP-2	ERBB1 CK-MB	CSK GAPDH, liver	SCFsR MMP-7	RGM-C Cadherin-6	0.883	0.805	1.687	0.904
74	RGM-C	CadherinE IL-17B	KPCI SCFsR	CK-MB IGFBP-2	ERBB1 NAGK	METAP1 Catalase	0.915	0.805	1.72	0.895
75	RGM-C	METAP1 CK-MB	SCFsR CNDP1	ERBB1 IMB1	YES b-ECGF	CadherinE CathepsinH	0.92	0.8	1.72	0.903
76	SCFsR	MMP-7 YES	CadherinE ERBB1	KPCI IL-17B	METAP1 HMG-1	CK-MB RGM-C	0.906	0.812	1.718	0.897
77	RGM-C	CadherinE SCFsR	HSP90a GAPDH, liver	CK-MB BMP-1	YES VEGF	ERBB1 LGMN	0.883	0.817	1.699	0.902

TABLE 10-continued

78	SCFsR	ERBB1	CadherinE	METAP1	RGM-C	MMR	0.906	0.814	1.72	0.909
		MK13	CK-MB	HSP90b	IGFBP-2	LRIG3				
79	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	0.915	0.81	1.725	0.892
		IL-17B	SCFsR	CNDP1	NACA	IGFBP-2				
80	YES	CadherinE	ERBB1	CSK	SCFsR	CK-MB	0.901	0.81	1.711	0.899
		MMP-7	KPCI	CNDP1	Prothrombin	Proteinase-3				
81	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.901	0.807	1.709	0.902
		CK-MB	MMR	GAPDH, liver	BLC	VEGF				
82	CadherinE	IGFBP-2	METAP1	ERBB1	RGM-C	HSP90a	0.915	0.807	1.723	0.907
		CK-MB	C9	SCFsR	YES	b-ECGF				
83	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.897	0.807	1.704	0.905
		MMP-7	GAPDH, liver	CK-MB	CATC	ApoA-I				
84	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	CadherinE	0.911	0.776	1.687	0.889
		IGFBP-2	NACA	VEGF	CK-MB	Cadherin-6				
85	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	0.93	0.79	1.72	0.899
		CK-MB	SCFsR	CNDP1	b-ECGF	Catalase				
86	CK-MB	SCFsR	METAP1	CadherinE	MMP-7	GAPDH, liver	0.925	0.795	1.72	0.91
		RGM-C	ERBB1	C9	YES	CathepsinH				
87	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.906	0.812	1.718	0.904
		CK-MB	BMP-1	HMG-1	HSP90b	MMR				
88	MMR	CSK	CadherinE	CK-MB	RGM-C	ERBB1	0.883	0.817	1.699	0.907
		GAPDH, liver	ApoA-I	YES	IGFBP-2	LGMN				
89	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	0.911	0.81	1.72	0.905
		MMR	SCFsR	MK13	CNDP1	BMP-1				
90	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.915	0.795	1.711	0.901
		CK-MB	CNDP1	KPCI	IGFBP-2	Proteinase-3				
91	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	0.906	0.814	1.72	0.898
		MMR	SCFsR	IGFBP-2	Prothrombin	CalpainI				
92	CD30Ligand	METAP1	CK-MB	ERBB1	CadherinE	YES	0.915	0.793	1.708	0.894
		RGM-C	IGFBP-2	SCFsR	KPCI	BLC				
93	CK-MB	IGFBP-2	CSK	CadherinE	RGM-C	ERBB1	0.897	0.807	1.704	0.898
		YES	FGF-17	GAPDH, liver	MMR	CATC				
94	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.892	0.793	1.685	0.895
		YES	SCFsR	KPCI	BMP-1	Cadherin-6				
95	RGM-C	C9	ERBB1	CadherinE	METAP1	SCFsR	0.901	0.817	1.718	0.909
		CK-MB	NAGK	IGFBP-2	b-ECGF	Catalase				
96	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.911	0.807	1.718	0.899
		MMP-7	GAPDH, liver	KPCI	ApoA-I	CathepsinH				
97	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.911	0.807	1.718	0.899
		CK-MB	BMP-1	HMG-1	KPCI	IGFBP-2				
98	CK-MB	SCFsR	METAP1	CadherinE	ERBB1	IGFBP-2	0.925	0.8	1.725	0.904
		YES	RGM-C	IMB1	BMP-1	b-ECGF				
99	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C	0.887	0.812	1.699	0.893
		CK-MB	CalpainI	Catalase	b-ECGF	LGMN				
100	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	MMR	0.906	0.814	1.72	0.907
		YES	RGM-C	CD30Ligand	LRIG3	CNDP1				

Marker	Count	Marker	Count	Marker	Count
CadherinE	100	b-ECGF	19	LGMN	8
ERBB1	99	HSP90a	14	IMB1	8
RGM-C	98	BMP-1	12	IL-17B	8
CK-MB	98	VEGF	11	HSP90b	8
SCFsR	92	ApoA-I	11	HMG-1	8
YES	81	CalpainI	10	CathepsinH	8
METAP1	53	FGF-17	9	Cadherin-6	8
GAPDH, liver	44	Catalase	9	CATC	8
IGFBP-2	43	CD30Ligand	9	BLC	8
CSK	37	C9	9	Prothrombin	7
CNDP1	35	NAGK	8	Proteinase-3	7
MMR	34	NACA	8	MK13	7
KPCI	28	LRIG3	8	MEK1	7
MMP-7	21				

TABLE 11

100 Panels of 12 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers						Sensitivity	Specificity	Sens. + Spec.	AUC
1	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	0.92	0.81	1.73	0.914
	METAP1	SCFsR	FGF-17	ApoA-I	YES	IGFBP-2				
2	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.892	0.821	1.713	0.903
	CK-MB	MMR	GAPDH, liver	BLC	VEGF	IGFBP-2				
3	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.901	0.829	1.73	0.914
	YES	GAPDH, liver	MMR	SCFsR	BMP-1	HMG-1				

TABLE 11-continued

4	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.925	0.807	1.732	0.906
	CK-MB	Catalase	NAGK	b-ECGF	C9	IGFBP-2				
5	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	0.925	0.795	1.72	0.902
	RGM-C	GAPDH, liver	FGF-17	IGFBP-2	CATC	SCFsR				
6	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.915	0.814	1.73	0.911
	CD30Ligand	CK-MB	FGF-17	GAPDH, liver	MMR	IGFBP-2				
7	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.892	0.807	1.699	0.9
	YES	SCFsR	GAPDH, liver	C9	LRIG3	Cadherin-6				
8	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C	0.915	0.812	1.727	0.899
	CK-MB	CSK	b-ECGF	CalpainI	IGFBP-2	CD30Ligand				
9	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.915	0.81	1.725	0.899
	CK-MB	BMP-1	HMG-1	KPCI	IGFBP-2	CathepsinH				
10	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	CadherinE	0.925	0.805	1.73	0.9
	IGFBP-2	KPCI	CK-MB	CNDP1	MK13	YES				
11	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CNDP1	0.915	0.807	1.723	0.904
	CSK	CK-MB	HSP90b	YES	b-ECGF	Catalase				
12	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.906	0.824	1.73	0.908
	YES	SCFsR	GAPDH, liver	FGF-17	IGFBP-2	IL-17B				
13	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	0.925	0.807	1.732	0.906
	MMR	CK-MB	IGFBP-2	MK13	YES	MEK1				
14	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.92	0.793	1.713	0.893
	CK-MB	CNDP1	NACA	HSP90a	b-ECGF	LGMN				
15	IL-17B	CadherinE	ERBB1	METAP1	CK-MB	RGM-C	0.925	0.805	1.73	0.913
	YES	SCFsR	GAPDH, liver	MMP-7	ApoA-I	IGFBP-2				
16	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.925	0.798	1.723	0.902
	CK-MB	CNDP1	NACA	b-ECGF	BMP-1	Proteinase-3				
17	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CD30Ligand	0.92	0.81	1.73	0.903
	YES	SCFsR	IGFBP-2	KPCI	Prothrombin	CNDP1				
18	MMR	CSK	CadherinE	CK-MB	RGM-C	ERBB1	0.897	0.817	1.713	0.904
	GAPDH, liver	ApoA-I	YES	SCFsR	LRIG3	BLC				
19	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.92	0.79	1.711	0.897
	CK-MB	CNDP1	NACA	IGFBP-2	MK13	CATC				
20	SCFsR	ERBB1	HSP90a	YES	CadherinE	IMB1	0.901	0.795	1.697	0.894
	CK-MB	GAPDH, liver	RGM-C	CNDP1	b-ECGF	Cadherin-6				
21	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C	0.92	0.807	1.727	0.91
	CK-MB	CSK	GAPDH, liver	b-ECGF	ApoA-I	LRIG3				
22	CathepsinH	CSK	ERBB1	RGM-C	CadherinE	SCFsR	0.92	0.802	1.723	0.902
	KPCI	Catalase	YES	CNDP1	CK-MB	Prothrombin				
23	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES	0.92	0.802	1.723	0.906
	METAP1	SCFsR	CK-MB	Catalase	CNDP1	IGFBP-2				
24	CK-MB	SCFsR	METAP1	CadherinE	ERBB1	IGFBP-2	0.915	0.79	1.706	0.896
	YES	RGM-C	HSP90a	CNDP1	NACA	LGMN				
25	CadherinE	IGFBP-2	METAP1	ERBB1	MK13	CK-MB	0.93	0.81	1.739	0.904
	SCFsR	MEK1	RGM-C	NACA	YES	CNDP1				
26	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.925	0.805	1.73	0.901
	CK-MB	CNDP1	NACA	MMP-7	GAPDH, liver	IL-17B				
27	RGM-C	C9	ERBB1	CadherinE	METAP1	SCFsR	0.911	0.814	1.725	0.907
	CK-MB	NAGK	IGFBP-2	b-ECGF	Catalase	VEGF				
28	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.925	0.793	1.718	0.9
	CK-MB	CNDP1	NACA	CathepsinH	b-ECGF	Proteinase-3				
29	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	0.906	0.805	1.711	0.904
	METAP1	C9	SCFsR	IGFBP-2	BLC	YES				
30	YES	CK-MB	ERBB1	CadherinE	METAP1	MMP-7	0.911	0.798	1.708	0.904
	IGFBP-2	RGM-C	SCFsR	GAPDH, liver	FGF-17	CATC				
31	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	MMR	0.887	0.807	1.694	0.901
	YES	RGM-C	C9	SCFsR	LRIG3	Cadherin-6				
32	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.911	0.814	1.725	0.905
	MMR	CK-MB	CalpainI	MK13	CNDP1	GAPDH, liver				
33	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.925	0.805	1.73	0.896
	CK-MB	CNDP1	NACA	HSP90a	HMG-1	b-ECGF				
34	RGM-C	BMP-1	ERBB1	METAP1	CadherinE	HSP90b	0.906	0.814	1.72	0.896
	SCFsR	CK-MB	YES	IMB1	Catalase	VEGF				
35	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	0.887	0.817	1.704	0.902
	BMP-1	SCFsR	RGM-C	VEGF	CD30Ligand	LGMN				
36	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.925	0.805	1.73	0.904
	CK-MB	CNDP1	NACA	IGFBP-2	MEK1	Catalase				
37	MMR	CSK	CadherinE	CK-MB	RGM-C	ERBB1	0.92	0.805	1.725	0.899
	KPCI	NAGK	SCFsR	CalpainI	LRIG3	IGFBP-2				
38	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	0.906	0.81	1.716	0.89
	IL-17B	SCFsR	CNDP1	NACA	IGFBP-2	Proteinase-3				
39	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	0.934	0.795	1.73	0.904
	CK-MB	SCFsR	CNDP1	b-ECGF	Prothrombin	RGM-C				
40	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.906	0.805	1.711	0.899
	CK-MB	Catalase	NAGK	b-ECGF	IGFBP-2	BLC				
41	METAP1	GAPDH, liver	MMP-7	CadherinE	ERBB1	YES	0.906	0.8	1.706	0.901
	CK-MB	SCFsR	FGF-17	RGM-C	Catalase	CATC				
42	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	0.892	0.802	1.694	0.9
	MMR	CK-MB	IGFBP-2	MK13	CNDP1	Cadherin-6				
43	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.92	0.802	1.723	0.9
	CK-MB	CNDP1	NACA	CathepsinH	b-ECGF	MEK1				

TABLE 11-continued

44	CNDP1	ERBB1	CadherinE	METAP1	CK-MB	YES	0.93	0.798	1.727	0.898
	NACA	IL-17B	IGFBP-2	RGM-C	SCFsR	HMG-1				
45	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	0.906	0.814	1.72	0.905
	HSP90b	SCFsR	YES	LRIG3	FGF-17	ApoA-I				
46	MMR	CSK	CadherinE	CK-MB	RGM-C	ERBB1	0.887	0.814	1.702	0.904
	GAPDH, liver	ApoA-I	YES	b-ECGF	IGFBP-2	LGMN				
47	CK-MB	MMR	GAPDH, liver	CadherinE	RGM-C	METAP1	0.906	0.81	1.716	0.909
	IGFBP-2	SCFsR	FGF-17	ERBB1	YES	Proteinase-3				
48	CK-MB	MMP-7	METAP1	RGM-C	SCFsR	CadherinE	0.93	0.798	1.727	0.901
	b-ECGF	YES	GAPDH, liver	CNDP1	Prothrombin	HSP90a				
49	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.92	0.79	1.711	0.897
	CK-MB	CNDP1	NACA	MMP-7	GAPDH, liver	BLC				
50	RGM-C	CK-MB	ERBB1	METAP1	FGF-17	CadherinE	0.915	0.79	1.706	0.897
	IGFBP-2	YES	MMR	SCFsR	IMB1	CATC				
51	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.92	0.807	1.727	0.903
	CK-MB	CNDP1	NACA	IGFBP-2	MEK1	CD30Ligand				
52	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.883	0.81	1.692	0.894
	YES	SCFsR	KPCI	MMR	FGF-17	Cadherin-6				
53	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C	0.915	0.81	1.725	0.897
	CK-MB	CSK	b-ECGF	CalpainI	IL-17B	BMP-1				
54	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.93	0.793	1.722	0.9
	CK-MB	CNDP1	NACA	CathepsinH	b-ECGF	Catalase				
55	YES	CadherinE	ERBB1	RGM-C	METAP1	NACA	0.92	0.802	1.723	0.902
	MMR	CK-MB	SCFsR	MK13	CNDP1	HMG-1				
56	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES	0.911	0.81	1.72	0.897
	METAP1	SCFsR	CK-MB	HSP90a	CNDP1	HMG-1				
57	SCFsR	ERBB1	HSP90a	YES	CadherinE	IMB1	0.892	0.81	1.702	0.896
	CK-MB	GAPDH, liver	RGM-C	CNDP1	b-ECGF	LGMN				
58	RGM-C	CK-MB	ERBB1	METAP1	FGF-17	CadherinE	0.92	0.805	1.725	0.9
	IGFBP-2	YES	MMR	NAGK	KPCI	SCFsR				
59	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	0.911	0.805	1.716	0.896
	CNDP1	Catalase	YES	ERBB1	MK13	Proteinase-3				
60	YES	CK-MB	ERBB1	CadherinE	METAP1	MMP-7	0.92	0.805	1.725	0.913
	IGFBP-2	RGM-C	SCFsR	GAPDH, liver	MEK1	Prothrombin				
61	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.93	0.805	1.734	0.911
	CK-MB	CNDP1	GAPDH, liver	b-ECGF	MMR	VEGF				
62	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	0.873	0.836	1.709	0.906
	CSK	MMR	IGFBP-2	BLC	ApoA-I	VEGF				
63	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	0.915	0.81	1.725	0.913
	RGM-C	GAPDH, liver	FGF-17	IGFBP-2	C9	SCFsR				
64	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	0.915	0.79	1.706	0.891
	CNDP1	Catalase	YES	ERBB1	MK13	CATC				
65	CD30Ligand	METAP1	CK-MB	ERBB1	CadherinE	YES	0.93	0.798	1.727	0.903
	RGM-C	IGFBP-2	SCFsR	b-ECGF	CNDP1	NACA				
66	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.897	0.795	1.692	0.894
	YES	SCFsR	KPCI	BMP-1	b-ECGF	Cadherin-6				
67	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	CadherinE	0.92	0.805	1.725	0.895
	IGFBP-2	KPCI	CK-MB	CNDP1	CalpainI	b-ECGF				
68	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	0.906	0.814	1.72	0.908
	RGM-C	GAPDH, liver	BMP-1	SCFsR	CathepsinH	MEK1				
69	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES	0.915	0.805	1.72	0.9
	METAP1	SCFsR	CK-MB	Catalase	CNDP1	HMG-1				
70	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C	0.897	0.805	1.701	0.892
	CK-MB	CSK	b-ECGF	CalpainI	Catalase	LGMN				
71	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.92	0.805	1.725	0.902
	CK-MB	FGF-17	NAGK	MMP-7	IGFBP-2	KPCI				
72	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	0.925	0.79	1.715	0.904
	CK-MB	SCFsR	RGM-C	b-ECGF	CNDP1	Proteinase-3				
73	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	0.906	0.817	1.723	0.9
	MMR	SCFsR	IGFBP-2	Prothrombin	MK13	GAPDH, liver				
74	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	0.873	0.836	1.709	0.904
	CSK	MMR	IGFBP-2	BLC	ApoA-I	MEK1				
75	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.92	0.805	1.725	0.902
	YES	SCFsR	GAPDH, liver	C9	NACA	CD30Ligand				
76	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.92	0.786	1.706	0.897
	CK-MB	CNDP1	NACA	MMP-7	GAPDH, liver	CATC				
77	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	0.897	0.795	1.692	0.889
	CNDP1	Catalase	YES	ERBB1	FGF-17	Cadherin-6				
78	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	0.915	0.805	1.72	0.898
	CNDP1	Catalase	YES	ERBB1	FGF-17	CathepsinH				
79	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES	0.925	0.795	1.72	0.906
	METAP1	SCFsR	CK-MB	BMP-1	CSK	MMP-7				
80	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	0.93	0.798	1.727	0.901
	CNDP1	CK-MB	VEGF	YES	IL-17B	Catalase				
81	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	0.92	0.781	1.701	0.897
	CK-MB	SCFsR	HSP90a	CNDP1	RGM-C	LGMN				
82	MMR	CSK	CadherinE	CK-MB	RGM-C	ERBB1	0.901	0.824	1.725	0.917
	GAPDH, liver	ApoA-I	YES	SCFsR	LRIG3	IGFBP-2				
83	SCFsR	NAGK	CadherinE	CK-MB	RGM-C	ERBB1	0.93	0.795	1.725	0.899
	IL-17B	METAP1	MMP-7	YES	IMB1	b-ECGF				

TABLE 11-continued

84	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	0.901	0.812	1.713	0.906
	RGM-C	GAPDH, liver	FGF-17	IGFBP-2	ApoA-I	Proteinase-3				
85	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	0.906	0.817	1.723	0.916
	IGFBP-2	RGM-C	Prothrombin	MMP-7	SCFsR	MEK1				
86	CadherinE	IGFBP-2	METAP1	ERBB1	RGM-C	HSP90a	0.897	0.812	1.709	0.901
	CK-MB	ApoA-I	YES	b-ECGF	SCFsR	BLC				
87	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.92	0.805	1.725	0.903
	YES	SCFsR	GAPDH, liver	C9	NACA	MEK1				
88	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	0.892	0.812	1.704	0.903
	YES	SCFsR	GAPDH, liver	FGF-17	IGFBP-2	CATC				
89	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	0.901	0.824	1.725	0.913
	IGFBP-2	RGM-C	CD30Ligand	ApoA-I	MEK1	SCFsR				
90	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.906	0.786	1.692	0.894
	CK-MB	NACA	CNDP1	b-ECGF	CathepsinH	Cadherin-6				
91	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	0.911	0.812	1.723	0.911
	BMP-1	RGM-C	MMR	CalpainI	ApoA-I	SCFsR				
92	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	0.934	0.788	1.722	0.9
	MMP-7	NACA	IL-17B	CK-MB	HMG-1	IGFBP-2				
93	CK-MB	SCFsR	METAP1	CadherinE	MMP-7	ERBB1	0.911	0.807	1.718	0.892
	RGM-C	Prothrombin	HSP90b	b-ECGF	NACA	HSP90a				
94	VEGF	METAP1	CadherinE	ERBB1	CK-MB	CalpainI	0.892	0.807	1.699	0.895
	CNDP1	RGM-C	SCFsR	MEK1	GAPDH, liver	LGMN				
95	YES	CadherinE	GAPDH, liver	MMP-7	SCFsR	CK-MB	0.906	0.817	1.723	0.912
	RGM-C	CSK	IGFBP-2	MMR	LRIG3	ApoA-I				
96	SCFsR	NAGK	CadherinE	CK-MB	RGM-C	ERBB1	0.911	0.812	1.723	0.904
	IL-17B	METAP1	MMP-7	CalpainI	ApoA-I	b-ECGF				
97	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	0.906	0.807	1.713	0.899
	CK-MB	NACA	CNDP1	b-ECGF	CD30Ligand	Proteinase-3				
98	CD30Ligand	METAP1	CK-MB	ERBB1	CadherinE	YES	0.901	0.807	1.709	0.9
	RGM-C	IGFBP-2	SCFsR	b-ECGF	BLC	GAPDH, liver				
99	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	0.92	0.805	1.725	0.913
	METAP1	C9	SCFsR	IGFBP-2	Catalase	FGF-17				
100	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	0.901	0.802	1.704	0.899
	RGM-C	GAPDH, liver	FGF-17	IGFBP-2	CATC	ApoA-I				

Marker	Count	Marker	Count
CadherinE	100	HSP90a	12
CK-MB	100	MK13	10
ERBB1	98	IL-17B	10
SCFsR	97	CalpainI	10
RGM-C	96	CD30Ligand	10
YES	84	BMP-1	10
METAP1	67	CATC	9
CNDP1	54	C9	9
IGFBP-2	53	BLC	9
GAPDH, liver	46	VEGF	8
b-ECGF	35	Prothrombin	8
MMR	32	Proteinase-3	8
CSK	31	NAGK	8
NACA	27	LRIG3	8
MMP-7	19	LGMN	8
KPCI	19	IMB1	8
FGF-17	19	HSP90b	8
Catalase	18	HMG-1	8
ApoA-I	16	CathepsinH	8
MEK1	12	Cadherin-6	8

TABLE 12

100 Panels of 13 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers							Sensitivity	Specificity	Sens. + Spec.	AUC
1	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.812	1.732	0.908
		CNDP1	GAPDH, liver	b-ECGF	BMP-1	IL-17B	ApoA-I				
2	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.79	1.715	0.897
		CNDP1	NACA	b-ECGF	IGFBP-2	Catalase	BLC				
3	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.802	1.727	0.911
		CNDP1	GAPDH, liver	b-ECGF	IGFBP-2	C9	Catalase				
4	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	CK-MB	0.92	0.798	1.718	0.898
		MMR	GAPDH, liver	NACA	CNDP1	MK13	CATC				
5	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	CSK	0.915	0.812	1.727	0.904
		MEK1	YES	CNDP1	IGFBP-2	NACA	CD30Ligand				

TABLE 12-continued

6	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.911	0.795	1.706	0.894
		Catalase	NAGK	b-ECGF	C9	IGFBP-2	Cadherin-6				
7	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C	CK-MB	0.901	0.824	1.725	0.904
		CSK	IGFBP-2	KPCI	MK13	CNDP1	Prothrombin				
8	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.8	1.725	0.902
		CNDP1	NACA	MMP-7	GAPDH, liver	CathepsinH	b-ECGF				
9	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	METAP1	0.92	0.81	1.73	0.911
		SCFsR	FGF-17	ApoA-I	YES	b-ECGF	IGFBP-2				
10	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	RGM-C	0.92	0.81	1.73	0.911
		GAPDH, liver	BMP-1	SCFsR	CNDP1	VEGF	HMG-1				
11	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	CSK	0.906	0.824	1.73	0.911
		MMR	IGFBP-2	CNDP1	YES	HSP90a	BMP-1				
12	CadherinE	METAP1	CK-MB	HSP90b	ERBB1	YES	SCFsR	0.925	0.8	1.725	0.904
		RGM-C	IGFBP-2	BMP-1	GAPDH, liver	Catalase	b-ECGF				
13	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	CNDP1	0.93	0.8	1.73	0.902
		CK-MB	HSP90a	b-ECGF	YES	ApoA-I	VEGF				
14	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.897	0.812	1.709	0.902
		SCFsR	RGM-C	VEGF	CD30Ligand	CNDP1	LGMN				
15	YES	CadherinE	ERBB1	RGM-C	CSK	CK-MB	LRIG3	0.897	0.826	1.723	0.912
		GAPDH, liver	MMR	BMP-1	SCFsR	ApoA-I	VEGF				
16	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.911	0.812	1.723	0.903
		Catalase	NAGK	b-ECGF	C9	IGFBP-2	Proteinase-3				
17	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	CK-MB	0.925	0.79	1.715	0.898
		SCFsR	CNDP1	b-ECGF	GAPDH, liver	RGM-C	BLC				
18	MMR	CSK	CadherinE	CK-MB	RGM-C	ERBB1	GAPDH, liver	0.911	0.805	1.716	0.904
		ApoA-I	YES	SCFsR	LRIG3	IGFBP-2	CATC				
19	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.892	0.812	1.704	0.902
		SCFsR	GAPDH, liver	Catalase	IGFBP-2	BMP-1	Cadherin-6				
20	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.906	0.819	1.725	0.91
		GAPDH, liver	MMR	b-ECGF	SCFsR	BMP-1	CalpainI				
21	CathepsinH	CSK	ERBB1	RGM-C	CadherinE	SCFsR	KPCI	0.92	0.802	1.723	0.9
		Catalase	YES	CNDP1	CK-MB	Prothrombin	HMG-1				
22	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	RGM-C	0.92	0.81	1.73	0.912
		GAPDH, liver	FGF-17	IGFBP-2	CNDP1	SCFsR	MK13				
23	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CD30Ligand	YES	0.911	0.812	1.723	0.898
		SCFsR	IGFBP-2	KPCI	Prothrombin	CNDP1	HSP90b				
24	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.805	1.725	0.899
		CNDP1	GAPDH, liver	b-ECGF	BMP-1	IL-17B	NACA				
25	RGM-C	CK-MB	ERBB1	METAP1	FGF-17	CadherinE	IGFBP-2	0.92	0.805	1.725	0.908
		YES	MMR	SCFsR	IMB1	CNDP1	b-ECGF				
26	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	CNDP1	0.906	0.802	1.708	0.9
		CK-MB	VEGF	YES	BMP-1	MK13	LGMN				
27	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	CSK	0.92	0.812	1.732	0.914
		MEK1	YES	CNDP1	IGFBP-2	ApoA-I	Catalase				
28	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	CK-MB	0.925	0.795	1.72	0.9
		SCFsR	CNDP1	b-ECGF	Prothrombin	ApoA-I	Proteinase-3				
29	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	CK-MB	0.892	0.821	1.713	0.904
		MMR	GAPDH, liver	BLC	VEGF	IGFBP-2	ApoA-I				
30	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	IGFBP-2	0.901	0.812	1.713	0.906
		CK-MB	GAPDH, liver	MMP-7	ApoA-I	LRIG3	CATC				
31	CD30Ligand	METAP1	CK-MB	ERBB1	CadherinE	YES	RGM-C	0.911	0.786	1.697	0.894
		IGFBP-2	SCFsR	b-ECGF	CNDP1	NACA	Cadherin-6				
32	SCFsR	ERBB1	CadherinE	METAP1	RGM-C	MMR	MK13	0.925	0.8	1.725	0.903
		IGFBP-2	CK-MB	NACA	ApoA-I	CalpainI	VEGF				
33	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.798	1.723	0.903
		CNDP1	NACA	IGFBP-2	MEK1	CathepsinH	Catalase				
34	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	CNDP1	0.911	0.814	1.725	0.9
		Catalase	YES	ERBB1	RGM-C	MEK1	HMG-1				
35	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.915	0.812	1.727	0.912
		SCFsR	GAPDH, liver	FGF-17	IGFBP-2	HSP90a	ApoA-I				
36	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	HSP90b	0.915	0.805	1.72	0.905
		SCFsR	YES	LRIG3	BMP-1	FGF-17	METAP1				
37	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	IL-17B	0.906	0.817	1.723	0.897
		SCFsR	IGFBP-2	CalpainI	CNDP1	Prothrombin	ApoA-I				
38	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C	CK-MB	0.897	0.81	1.706	0.897
		CSK	b-ECGF	CalpainI	MMR	BMP-1	LGMN				
39	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	CK-MB	0.93	0.8	1.73	0.905
		SCFsR	RGM-C	FGF-17	NAGK	IGFBP-2	CNDP1				

TABLE 12-continued

40	RGM-C	METAP1 CNDP1	SCFsR NACA	ERBB1 b-ECGF	YES IGFBP-2	CadherinE Catalase	CK-MB Proteinase-3	0.925	0.795	1.72	0.902
41	RGM-C	METAP1 Catalase	SCFsR MMP-7	ERBB1 GAPDH, liver	YES CNDP1	CadherinE b-ECGF	CK-MB BLC	0.911	0.802	1.713	0.904
42	YES	NAGK CK-MB	ERBB1 b-ECGF	HSP90a SCFsR	RGM-C C9	CadherinE IGFBP-2	METAP1 ApoA-I	0.925	0.8	1.725	0.906
43	MMR	ERBB1 GAPDH, liver	METAP1 FGF-17	CK-MB IGFBP-2	CadherinE CATC	YES SCFsR	RGM-C Catalase	0.915	0.798	1.713	0.9
44	RGM-C	METAP1 CNDP1	SCFsR NACA	ERBB1 b-ECGF	YES IGFBP-2	CadherinE Catalase	CK-MB Cadherin-6	0.915	0.781	1.696	0.895
45	SCFsR	ERBB1 CK-MB	CadherinE Catalase	METAP1 b-ECGF	IMB1 YES	RGM-C CathepsinH	CNDP1 MEK1	0.925	0.798	1.723	0.901
46	RGM-C	CadherinE SCFsR	KPCI MK13	CK-MB HMG-1	ERBB1 CNDP1	METAP1 BMP-1	MMR YES	0.911	0.814	1.725	0.903
47	RGM-C	CadherinE CK-MB	ERBB1 HSP90b	GAPDH, liver YES	SCFsR HSP90a	CNDP1 LRIG3	CSK b-ECGF	0.906	0.812	1.718	0.902
48	IL-17B	CadherinE SCFsR	ERBB1 GAPDH, liver	METAP1 CNDP1	CK-MB b-ECGF	RGM-C NACA	YES MMP-7	0.915	0.807	1.723	0.901
49	CD30Ligand	KPCI YES	ERBB1 CNDP1	SCFsR Prothrombin	CadherinE CathepsinH	CK-MB RGM-C	CSK LGMN	0.906	0.8	1.706	0.895
50	MMP-7	ERBB1 SCFsR	YES CNDP1	METAP1 b-ECGF	CadherinE Prothrombin	NACA FGF-17	CK-MB Proteinase-3	0.92	0.798	1.718	0.897
51	b-ECGF	CadherinE SCFsR	ERBB1 ApoA-I	METAP1 YES	RGM-C GAPDH, liver	CK-MB IGFBP-2	MMP-7 BLC	0.911	0.802	1.713	0.907
52	YES	CadherinE VEGF	ERBB1 GAPDH, liver	CSK MMR	SCFsR IGFBP-2	RGM-C HSP90a	CK-MB C9	0.901	0.821	1.723	0.909
53	MMR	ERBB1 GAPDH, liver	METAP1 FGF-17	CK-MB IGFBP-2	CadherinE CATC	YES SCFsR	RGM-C ApoA-I	0.915	0.795	1.711	0.904
54	RGM-C	CK-MB SCFsR	ERBB1 GAPDH, liver	CSK b-ECGF	CadherinE CalpainI	CNDP1 BMP-1	YES Cadherin-6	0.892	0.802	1.694	0.898
55	RGM-C	METAP1 BMP-1	SCFsR HMG-1	ERBB1 KPCI	YES IGFBP-2	CadherinE CNDP1	CK-MB Prothrombin	0.915	0.81	1.725	0.901
56	RGM-C	BMP-1 CK-MB	ERBB1 YES	METAP1 IMB1	CadherinE Catalase	HSP90b VEGF	SCFsR Prothrombin	0.906	0.812	1.718	0.895
57	IL-17B	CadherinE SCFsR	ERBB1 GAPDH, liver	METAP1 MMP-7	CK-MB IGFBP-2	RGM-C NACA	YES CNDP1	0.92	0.802	1.723	0.903
58	MMR	CSK ApoA-I	CadherinE BMP-1	CK-MB YES	RGM-C IGFBP-2	ERBB1 b-ECGF	GAPDH, liver LGMN	0.892	0.812	1.704	0.904
59	RGM-C	METAP1 CNDP1	SCFsR NACA	ERBB1 b-ECGF	YES BMP-1	CadherinE NAGK	CK-MB MMP-7	0.93	0.798	1.727	0.904
60	RGM-C	METAP1 CNDP1	SCFsR NACA	ERBB1 IGFBP-2	YES MEK1	CadherinE b-ECGF	CK-MB Proteinase-3	0.915	0.8	1.715	0.901
61	RGM-C	C9 NAGK	ERBB1 IGFBP-2	CadherinE b-ECGF	METAP1 Catalase	SCFsR VEGF	CK-MB BLC	0.901	0.81	1.711	0.899
62	MMR	ERBB1 SCFsR	GAPDH, liver FGF-17	CadherinE ApoA-I	RGM-C YES	CK-MB IGFBP-2	METAP1 CATC	0.915	0.795	1.711	0.904
63	RGM-C	CK-MB SCFsR	ERBB1 GAPDH, liver	CSK b-ECGF	CadherinE CalpainI	CNDP1 BMP-1	YES CD30Ligand	0.906	0.817	1.723	0.907
64	CD30Ligand	KPCI YES	ERBB1 CNDP1	SCFsR Prothrombin	CadherinE CathepsinH	CK-MB RGM-C	CSK Cadherin-6	0.897	0.798	1.694	0.893
65	RGM-C	METAP1 CNDP1	SCFsR KPCI	ERBB1 IGFBP-2	YES FGF-17	CadherinE BMP-1	CK-MB HMG-1	0.915	0.807	1.723	0.902
66	RGM-C	METAP1 CNDP1	SCFsR GAPDH, liver	ERBB1 b-ECGF	YES BMP-1	CadherinE MMP-7	CK-MB HSP90b	0.911	0.807	1.718	0.908
67	CNDP1	ERBB1 IL-17B	CadherinE IGFBP-2	METAP1 RGM-C	CK-MB SCFsR	YES HMG-1	NACA MEK1	0.92	0.802	1.723	0.898
68	MMR	ERBB1 YES	GAPDH, liver BMP-1	CadherinE CNDP1	RGM-C VEGF	CSK IMB1	SCFsR CK-MB	0.92	0.805	1.725	0.91
69	VEGF	RGM-C GAPDH, liver	ERBB1 SCFsR	METAP1 IGFBP-2	CK-MB YES	CadherinE ApoA-I	MMR LGMN	0.901	0.802	1.704	0.905
70	MMR	CSK ApoA-I	CadherinE YES	CK-MB SCFsR	RGM-C LRIG3	ERBB1 IGFBP-2	GAPDH, liver MEK1	0.901	0.821	1.723	0.912
71	RGM-C	METAP1 NACA	SCFsR CK-MB	ERBB1 CNDP1	HSP90a b-ECGF	CadherinE YES	IGFBP-2 Proteinase-3	0.92	0.795	1.715	0.899
72	RGM-C	METAP1 NACA	SCFsR CK-MB	ERBB1 NAGK	HSP90a MMP-7	CadherinE Prothrombin	b-ECGF BLC	0.92	0.79	1.711	0.891
73	RGM-C	METAP1 CNDP1	SCFsR GAPDH, liver	ERBB1 b-ECGF	YES IGFBP-2	CadherinE MEK1	CK-MB C9	0.906	0.817	1.723	0.91

TABLE 12-continued

74	CK-MB	IGFBP-2	CSK	CadherinE	RGM-C	ERBB1	YES	0.897	0.812	1.709	0.903
		FGF-17	GAPDH, liver	MMR	ApoA-I	SCFsR	CATC				
75	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	MMP-7	0.906	0.788	1.694	0.898
		GAPDH, liver	NACA	CNDP1	CK-MB	b-ECGF	Cadherin-6				
76	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.798	1.723	0.891
		CNDP1	NACA	CathepsinH	b-ECGF	Catalase	KPCI				
77	CK-MB	MMP-7	METAP1	RGM-C	SCFsR	CadherinE	b-ECGF	0.911	0.807	1.718	0.905
		YES	GAPDH, liver	CNDP1	ERBB1	HSP90b	Prothrombin				
78	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.93	0.793	1.722	0.902
		CNDP1	NACA	MMP-7	GAPDH, liver	ApoA-I	IL-17B				
79	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	CNDP1	0.911	0.812	1.723	0.908
		CK-MB	VEGF	YES	BMP-1	MMR	MK13				
80	YES	NAGK	ERBB1	HSP90a	RGM-C	CadherinE	METAP1	0.906	0.798	1.704	0.896
		CK-MB	b-ECGF	SCFsR	C9	ApoA-I	LGMN				
81	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	METAP1	0.92	0.802	1.723	0.914
		C9	SCFsR	YES	LRIG3	ApoA-I	IGFBP-2				
82	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	IGFBP-2	0.901	0.812	1.713	0.91
		CK-MB	GAPDH, liver	MMR	Catalase	ApoA-I	Proteinase-3				
83	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	CNDP1	0.915	0.793	1.708	0.897
		Catalase	YES	ERBB1	MK13	RGM-C	BLC				
84	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.783	1.708	0.896
		CNDP1	NACA	MMP-7	GAPDH, liver	CathepsinH	CATC				
85	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	CSK	0.911	0.812	1.723	0.906
		MMR	IGFBP-2	CNDP1	YES	KPCI	CD30Ligand				
86	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CSK	SCFsR	0.878	0.814	1.692	0.902
		YES	BMP-1	CNDP1	Catalase	CK-MB	Cadherin-6				
87	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	CSK	0.897	0.824	1.721	0.907
		MEK1	YES	BMP-1	CalpainI	CNDP1	b-ECGF				
88	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	MMP-7	0.92	0.8	1.72	0.902
		NACA	IL-17B	CK-MB	HMG-1	CNDP1	IGFBP-2				
89	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.915	0.802	1.718	0.901
		CNDP1	GAPDH, liver	b-ECGF	BMP-1	IL-17B	HSP90b				
90	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.911	0.812	1.723	0.895
		CNDP1	NACA	MMP-7	IMB1	HSP90a	ApoA-I				
91	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	METAP1	0.892	0.81	1.702	0.905
		SCFsR	FGF-17	ApoA-I	YES	IGFBP-2	LGMN				
92	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	IGFBP-2	0.892	0.829	1.721	0.915
		CK-MB	GAPDH, liver	MMP-7	ApoA-I	LRIG3	BMP-1				
93	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.901	0.812	1.713	0.904
		CNDP1	CalpainI	b-ECGF	BMP-1	VEGF	Proteinase-3				
94	YES	CK-MB	ERBB1	CadherinE	METAP1	MMP-7	IGFBP-2	0.915	0.793	1.708	0.902
		RGM-C	SCFsR	GAPDH, liver	NAGK	Prothrombin	BLC				
95	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	CK-MB	0.93	0.779	1.708	0.899
		SCFsR	RGM-C	b-ECGF	CNDP1	IGFBP-2	CATC				
96	METAP1	GAPDH, liver	MMP-7	CadherinE	CK-MB	RGM-C	FGF-17	0.915	0.807	1.723	0.907
		ERBB1	SCFsR	b-ECGF	YES	Prothrombin	CD30Ligand				
97	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.901	0.79	1.692	0.895
		CNDP1	NACA	b-ECGF	MMR	FGF-17	Cadherin-6				
98	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.93	0.793	1.722	0.903
		SCFsR	RGM-C	KPCI	CNDP1	CathepsinH	Catalase				
99	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	CNDP1	0.92	0.8	1.72	0.906
		CK-MB	VEGF	YES	IGFBP-2	HMG-1	BMP-1				
100	RGM-C	BMP-1	ERBB1	METAP1	CadherinE	HSP90b	SCFsR	0.915	0.802	1.718	0.898
		CK-MB	YES	VEGF	CSK	Catalase	GAPDH, liver				

Marker	Count	Marker	Count
ERBB1	100	FGF-17	15
CadherinE	100	Prothrombin	14
CK-MB	100	MEK1	10
SCFsR	99	HSP90a	10
RGM-C	98	NAGK	9
YES	94	IMB1	9
CNDP1	69	IL-17B	9
METAP1	67	HSP90b	9
GAPDH, liver	56	HMG-1	9
IGFBP-2	54	CathepsinH	9
b-ECGF	45	CalpainI	9
CSK	34	Cadherin-6	9
MMR	31	CD30Ligand	9

TABLE 12-continued

BMP-1	31	CATC	9
NACA	29	C9	9
ApoA-I	27	BLC	9
MMP-7	23	Proteinase-3	8
Catalase	23	MK13	8
VEGF	16	LRIG3	8
KPCI	15	LGMN	8

TABLE 13

100 Panels of 14 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers							Sensitivity	Specificity	Sens. + Spec.	AUC
1	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	RGM-C	0.93	0.802	1.732	0.915
	GAPDH, liver	BMP-1	SCFsR	CNDP1	VEGF	Catalase	ApoA-I				
2	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	LRIG3	0.911	0.805	1.716	0.904
	RGM-C	IGFBP-2	FGF-17	GAPDH, liver	SCFsR	ApoA-I	BLC				
3	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	VEGF	RGM-C	0.906	0.819	1.725	0.91
	CSK	CNDP1	MEK1	SCFsR	C9	Catalase	IGFBP-2				
4	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.93	0.79	1.72	0.896
	CNDP1	NACA	MMP-7	GAPDH, liver	CathepsinH	b-ECGF	CATC				
5	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	CSK	0.925	0.807	1.732	0.905
	MMR	IGFBP-2	CNDP1	YES	KPCI	MEK1	CD30Ligand				
6	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.897	0.814	1.711	0.902
	SCFsR	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	Cadherin-6				
7	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.925	0.81	1.734	0.909
	SCFsR	RGM-C	CNDP1	VEGF	Prothrombin	CalpainI	b-ECGF				
8	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.915	0.821	1.737	0.913
	SCFsR	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	HMG-1				
9	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.93	0.795	1.725	0.904
	CNDP1	NACA	HSP90a	ApoA-I	MMP-7	Prothrombin	b-ECGF				
10	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.802	1.727	0.897
	CNDP1	KPCI	b-ECGF	BMP-1	Prothrombin	IGFBP-2	HSP90b				
11	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C	CK-MB	0.92	0.805	1.725	0.9
	CSK	GAPDH, liver	b-ECGF	IGFBP-2	NACA	IL-17B	ApoA-I				
12	RGM-C	CK-MB	ERBB1	IMB1	CadherinE	YES	SCFsR	0.911	0.819	1.73	0.902
	MMR	CSK	CNDP1	MK13	Prothrombin	IGFBP-2	KPCI				
13	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	CNDP1	0.915	0.795	1.711	0.901
	CK-MB	Catalase	b-ECGF	VEGF	YES	BMP-1	LGMN				
14	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	CK-MB	0.92	0.807	1.727	0.901
	NACA	CNDP1	b-ECGF	CD30Ligand	MEK1	IGFBP-2	NAGK				
15	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.795	1.72	0.904
	Catalase	MMP-7	GAPDH, liver	CNDP1	IGFBP-2	NACA	Proteinase-3				
16	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.883	0.831	1.714	0.903
	SCFsR	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	BLC				
17	CK-MB	MMR	GAPDH, liver	CadherinE	RGM-C	METAP1	IGFBP-2	0.92	0.805	1.725	0.911
	SCFsR	YES	ERBB1	b-ECGF	ApoA-I	C9	FGF-17				
18	CK-MB	MMR	GAPDH, liver	CadherinE	RGM-C	METAP1	IGFBP-2	0.911	0.8	1.711	0.903
	SCFsR	YES	ERBB1	b-ECGF	ApoA-I	C9	CATC				
19	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.887	0.814	1.702	0.9
	GAPDH, liver	MMR	b-ECGF	SCFsR	BMP-1	CalpainI	Cadherin-6				
20	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	CNDP1	0.92	0.81	1.73	0.9
	Catalase	YES	ERBB1	RGM-C	BMP-1	CalpainI	CathepsinH				
21	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.81	1.73	0.903
	BMP-1	HMG-1	KPCI	IGFBP-2	CNDP1	GAPDH, liver	MMR				
22	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.802	1.723	0.894
	CNDP1	NACA	VEGF	IL-17B	GAPDH, liver	b-ECGF	HSP90a				
23	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.802	1.723	0.903
	Catalase	MMP-7	GAPDH, liver	CNDP1	b-ECGF	NAGK	HSP90b				
24	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C	CNDP1	0.901	0.807	1.709	0.899
	CK-MB	VEGF	YES	BMP-1	MK13	LRIG3	LGMN				
25	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.915	0.802	1.718	0.901
	CNDP1	NACA	IGFBP-2	MEK1	Catalase	Proteinase-3	b-ECGF				
26	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C	CK-MB	0.911	0.802	1.713	0.891
	CSK	b-ECGF	CalpainI	IGFBP-2	CD30Ligand	Prothrombin	BLC				
27	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	METAP1	0.906	0.802	1.708	0.902
	SCFsR	FGF-17	ApoA-I	YES	IGFBP-2	CATC	LRIG3				

TABLE 13-continued

28	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	VEGF	RGM-C	0.873	0.826	1.699	0.899
	CSK	CNDP1	MEK1	SCFsR	BMP-1	IGFBP-2	Cadherin-6				
29	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.93	0.795	1.725	0.899
	CNDP1	GAPDH, liver	b-ECGF	BMP-1	KPCI	CathepsinH	Catalase				
30	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.897	0.831	1.728	0.91
	SCFsR	RGM-C	CNDP1	VEGF	HMG-1	IGFBP-2	b-ECGF				
31	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	RGM-C	0.92	0.802	1.723	0.902
	GAPDH, liver	BMP-1	SCFsR	KPCI	IGFBP-2	CNDP1	HSP90a				
32	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.798	1.723	0.905
	CNDP1	GAPDH, liver	b-ECGF	IGFBP-2	Catalase	HSP90b	C9				
33	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.8	1.725	0.903
	CNDP1	NACA	VEGF	IL-17B	GAPDH, liver	MMP-7	ApoA-I				
34	CK-MB	MMR	GAPDH, liver	CadherinE	RGM-C	METAP1	IGFBP-2	0.911	0.798	1.708	0.905
	SCFsR	YES	ERBB1	b-ECGF	ApoA-I	C9	LGMN				
35	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	VEGF	RGM-C	0.887	0.843	1.73	0.908
	CSK	CNDP1	MEK1	SCFsR	BMP-1	MK13	IGFBP-2				
36	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.802	1.727	0.909
	Catalase	MMP-7	GAPDH, liver	CNDP1	b-ECGF	NAGK	FGF-17				
37	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.883	0.833	1.716	0.907
	SCFsR	RGM-C	CNDP1	VEGF	CathepsinH	IGFBP-2	Proteinase-3				
38	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.901	0.81	1.711	0.905
	Catalase	MMP-7	GAPDH, liver	CNDP1	b-ECGF	BLC	IGFBP-2				
39	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	METAP1	0.915	0.793	1.708	0.904
	C9	SCFsR	YES	LRIG3	ApoA-I	IGFBP-2	CATC				
40	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.805	1.73	0.911
	Catalase	MMP-7	GAPDH, liver	CNDP1	b-ECGF	ApoA-I	CD30Ligand				
41	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.883	0.814	1.697	0.9
	SCFsR	GAPDH, liver	Catalase	IGFBP-2	BMP-1	FGF-17	Cadherin-6				
42	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.892	0.833	1.725	0.91
	SCFsR	RGM-C	CNDP1	VEGF	HMG-1	IGFBP-2	MEK1				
43	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.798	1.723	0.898
	CNDP1	NACA	HSP90a	ApoA-I	VEGF	b-ECGF	GAPDH, liver				
44	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES	METAP1	0.925	0.798	1.723	0.905
	SCFsR	CK-MB	BMP-1	CNDP1	GAPDH, liver	Catalase	VEGF				
45	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	CK-MB	0.93	0.795	1.725	0.902
	SCFsR	RGM-C	FGF-17	NAGK	IGFBP-2	IL-17B	CNDP1				
46	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.81	1.73	0.897
	CNDP1	KPCI	b-ECGF	BMP-1	Prothrombin	IGFBP-2	IMB1				
47	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CNDP1	CK-MB	0.915	0.793	1.708	0.899
	METAP1	VEGF	YES	HSP90a	b-ECGF	ApoA-I	LGMN				
48	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.805	1.73	0.904
	CNDP1	KPCI	MMR	MK13	Prothrombin	MEK1	IGFBP-2				
49	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	VEGF	RGM-C	0.883	0.833	1.716	0.907
	CSK	CNDP1	MEK1	SCFsR	BMP-1	IGFBP-2	Proteinase-3				
50	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.915	0.795	1.711	0.895
	CNDP1	NACA	b-ECGF	IGFBP-2	Catalase	BLC	CD30Ligand				
51	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CSK	SCFsR	0.92	0.788	1.708	0.898
	YES	BMP-1	CNDP1	VEGF	IMB1	ApoA-I	CATC				
52	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	CK-MB	0.897	0.8	1.697	0.893
	NACA	CNDP1	b-ECGF	CD30Ligand	MEK1	IGFBP-2	Cadherin-6				
53	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	CNDP1	0.93	0.795	1.725	0.902
	Catalase	YES	ERBB1	RGM-C	BMP-1	GAPDH, liver	CathepsinH				
54	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.915	0.807	1.723	0.906
	GAPDH, liver	MMR	SCFsR	BMP-1	HMG-1	KPCI	IGFBP-2				
55	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES	METAP1	0.925	0.795	1.72	0.905
	SCFsR	CK-MB	Catalase	CNDP1	HMG-1	IGFBP-2	C9				
56	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.798	1.723	0.899
	CNDP1	GAPDH, liver	b-ECGF	BMP-1	IL-17B	IMB1	CD30Ligand				
57	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.892	0.814	1.706	0.907
	SCFsR	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	LGMN				
58	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.911	0.814	1.725	0.909
	SCFsR	GAPDH, liver	b-ECGF	CalpainI	BMP-1	LRIG3	ApoA-I				
59	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR	CNDP1	0.92	0.807	1.727	0.9
	Catalase	YES	ERBB1	MK13	RGM-C	MMR	IMB1				
60	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.802	1.727	0.905
	CNDP1	NACA	MMP-7	NAGK	b-ECGF	IGFBP-2	FGF-17				

TABLE 13-continued

61	RGM-C	C9	ERBB1	CadherinE	METAP1	SCFsR	CK-MB	0.901	0.814	1.716	0.905
	NAGK	IGFBP-2	b-ECGF	Catalase	VEGF	Proteinase-3	ApoA-I				
62	CK-MB	SCFsR	METAP1	CadherinE	ERBB1	IGFBP-2	YES	0.915	0.795	1.711	0.901
	RGM-C	HSP90a	CNDP1	ApoA-I	GAPDH, liver	FGF-17	BLC				
63	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.911	0.795	1.706	0.901
	GAPDH, liver	MMR	SCFsR	BMP-1	MK13	IMB1	CATC				
64	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.883	0.812	1.695	0.901
	RGM-C	MMR	CalpainI	ApoA-I	SCFsR	CNDP1	Cadherin-6				
65	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.798	1.723	0.901
	CNDP1	NACA	IGFBP-2	MEK1	Catalase	HMG-1	CathepsinH				
66	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB	HSP90b	0.915	0.802	1.718	0.906
	SCFsR	YES	LRIG3	BMP-1	FGF-17	ApoA-I	METAP1				
67	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.911	0.81	1.72	0.909
	SCFsR	GAPDH, liver	Catalase	IGFBP-2	MMP-7	Prothrombin	IL-17B				
68	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	CK-MB	0.897	0.81	1.706	0.9
	MMR	KPCI	MEK1	GAPDH, liver	CNDP1	BMP-1	LGMN				
69	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	CK-MB	0.915	0.8	1.715	0.904
	SCFsR	RGM-C	b-ECGF	CNDP1	IGFBP-2	Prothrombin	Proteinase-3				
70	RGM-C	CadherinE	MMR	GAPDH, liver	IGFBP-2	ERBB1	METAP1	0.92	0.79	1.711	0.892
	CK-MB	SCFsR	NACA	HSP90a	b-ECGF	Prothrombin	BLC				
71	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.915	0.79	1.706	0.905
	Catalase	MMP-7	GAPDH, liver	CNDP1	IGFBP-2	FGF-17	CATC				
72	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	CK-MB	0.883	0.812	1.695	0.897
	MMR	KPCI	MEK1	GAPDH, liver	CNDP1	BMP-1	Cadherin-6				
73	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES	BMP-1	0.887	0.833	1.721	0.907
	SCFsR	RGM-C	VEGF	CD30Ligand	CathepsinH	IGFBP-2	CNDP1				
74	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.798	1.718	0.906
	CNDP1	GAPDH, liver	b-ECGF	IGFBP-2	Catalase	HSP90b	BMP-1				
75	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	IL-17B	0.911	0.81	1.72	0.898
	SCFsR	IGFBP-2	CalpainI	CNDP1	Prothrombin	ApoA-I	BMP-1				
76	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.906	0.8	1.706	0.901
	GAPDH, liver	MMR	SCFsR	FGF-17	KPCI	BMP-1	LGMN				
77	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C	CK-MB	0.915	0.81	1.725	0.905
	MMR	GAPDH, liver	NACA	CNDP1	MK13	MEK1	LRIG3				
78	YES	CadherinE	KPCI	CK-MB	ERBB1	METAP1	MMP-7	0.925	0.802	1.727	0.902
	CNDP1	SCFsR	MK13	RGM-C	Prothrombin	IGFBP-2	NAGK				
79	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.915	0.8	1.715	0.904
	CNDP1	NACA	MMP-7	MEK1	IGFBP-2	Prothrombin	Proteinase-3				
80	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.79	1.711	0.896
	CNDP1	NACA	b-ECGF	IGFBP-2	Catalase	BLC	HMG-1				
81	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C	CK-MB	0.915	0.79	1.706	0.896
	CSK	GAPDH, liver	b-ECGF	IGFBP-2	NACA	CNDP1	CATC				
82	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.901	0.793	1.694	0.9
	GAPDH, liver	MMR	b-ECGF	SCFsR	IMB1	BMP-1	Cadherin-6				
83	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.915	0.805	1.72	0.901
	CNDP1	NACA	MMP-7	GAPDH, liver	CathepsinH	Prothrombin	b-FCGF				
84	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	CadherinE	IGFBP-2	0.925	0.798	1.723	0.901
	NACA	CK-MB	ApoA-I	MMR	NAGK	b-ECGF	LRIG3				
85	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES	METAP1	0.92	0.798	1.718	0.901
	SCFsR	CK-MB	BMP-1	CNDP1	GAPDH, liver	Catalase	NAGK				
86	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.92	0.8	1.72	0.9
	CNDP1	NACA	VEGF	IL-17B	GAPDH, liver	b-ECGF	BMP-1				
87	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.911	0.795	1.706	0.896
	CNDP1	NACA	HSP90a	ApoA-I	MMP-7	GAPDH, liver	LGMN				
88	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.925	0.79	1.715	0.904
	CNDP1	NACA	b-ECGF	IGFBP-2	Catalase	BMP-1	Proteinase-3				
89	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.93	0.781	1.711	0.895
	CNDP1	NACA	b-ECGF	IGFBP-2	Catalase	BLC	CSK				
90	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.93	0.795	1.725	0.913
	CNDP1	GAPDH, liver	b-ECGF	IGFBP-2	C9	MMP-7	Catalase				
91	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA	CK-MB	0.92	0.786	1.706	0.894
	SCFsR	CNDP1	b-ECGF	FGF-17	IGFBP-2	GAPDH, liver	CATC				
92	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB	CSK	0.92	0.807	1.727	0.904
	MEK1	YES	CNDP1	IGFBP-2	NACA	MMR	CD30Ligand				
93	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	RGM-C	0.901	0.793	1.694	0.895
	IGFBP-2	MK13	SCFsR	KPCI	CNDP1	Prothrombin	Cadherin-6				
94	RGM-C	METAP1	SCFsR	ERBB1	HSP90a	CadherinE	VEGF	0.92	0.8	1.72	0.901
	CK-MB	YES	BMP-1	NACA	ApoA-I	Prothrombin	CathepsinH				
95	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.915	0.807	1.723	0.899
	CNDP1	KPCI	IGFBP-2	FGF-17	BMP-1	HMG-1	NAGK				

TABLE 13-continued

96	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE	CK-MB	0.906	0.81	1.716	0.899
	CNDP1	CalpainI	b-ECGF	BMP-1	GAPDH, liver	VEGF	HSP90b				
97	RGM-C	CadherinE	KPCI	CK-MB	ERBB1	METAP1	IL-17B	0.92	0.8	1.72	0.897
	SCFsR	CNDP1	IGFBP-2	IMB1	MMR	YES	Catalase				
98	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.887	0.817	1.704	0.905
	SCFsR	GAPDH, liver	Catalase	IGFBP-2	BMP-1	b-ECGF	LGMN				
99	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES	LRIG3	0.92	0.802	1.723	0.912
	RGM-C	IGFBP-2	FGF-17	GAPDH, liver	SCFsR	ApoA-I	C9				
100	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1	YES	0.897	0.817	1.713	0.907
	SCFsR	GAPDH, liver	Catalase	MEK1	IGFBP-2	C9	Proteinase-3				

Marker	Count	Marker	Count
SCFsR	100	MEK1	17
ERBB1	100	Prothrombin	16
CadherinE	100	FGF-17	14
RGM-C	99	C9	11
CK-MB	99	NAGK	10
YES	93	IMB1	10
CNDP1	87	HSP90a	10
GAPDH, liver	69	CalpainI	10
IGFBP-2	67	Proteinase-3	9
METAP1	64	MK13	9
b-ECGF	48	LRIG3	9
BMP-1	45	LGMN	9
CSK	37	IL-17B	9
Catalase	35	HSP90b	9
MMR	32	HMG-1	9
NACA	29	CathepsinH	9
VEGF	26	Cadherin-6	9
ApoA-I	24	CD30Ligand	9
KPCI	21	CATC	9
MMP-7	19	BLC	9

TABLE 14

100 Panels of 15 Benign vs. Cancerous Nodule Biomarkers

	Biomarkers					
1	b-ECGF	CadherinE	ERBB1	METAP1	RGM-C	CK-MB
	ApoA-I	YES	GAPDH, liver	IGFBP-2	CNDP1	Prothrombin
2	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES
	RGM-C	CNDP1	VEGF	HMG-1	IGFBP-2	b-ECGF
3	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	MMP-7	GAPDH, liver	CNDP1	b-ECGF	ApoA-I	Prothrombin
4	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES
	CK-MB	BMP-1	CNDP1	GAPDH, liver	Catalase	VEGF
5	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	CD30Ligand	CK-MB	NAGK	IGFBP-2	Prothrombin	CNDP1
6	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA
	RGM-C	b-ECGF	CNDP1	IGFBP-2	Prothrombin	ApoA-I
7	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C
	IGFBP-2	KPCI	MK13	ApoA-I	CNDP1	GAPDH, liver
8	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	MMP-7	GAPDH, liver	CathepsinH	Catalase	b-ECGF
9	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	MMR	b-ECGF	SCFsR	IMB1	BMP-1	FGF-17
10	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	HSP90a	ApoA-I	MMP-7	Prothrombin	b-ECGF
11	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C
	GAPDH, liver	b-ECGF	IGFBP-2	NACA	CNDP1	LRIG3
12	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES
	RGM-C	CNDP1	VEGF	Catalase	ApoA-I	C9
13	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	MMR	SCFsR	BMP-1	MK13	KPCI	Prothrombin
14	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	b-ECGF	MMR	GAPDH, liver	IGFBP-2	BMP-1
15	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB
	SCFsR	IGFBP-2	Catalase	FGF-17	b-ECGF	YES
16	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	CD30Ligand	Prothrombin	MMP-7	b-ECGF	GAPDH, liver
17	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	b-ECGF	MMR	GAPDH, liver	IGFBP-2	BMP-1
18	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	b-ECGF	BMP-1	GAPDH, liver	Catalase	CathepsinH

TABLE 14-continued

19	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES
	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	FGF-17
20	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA
	RGM-C	b-ECGF	CNDP1	IGFBP-2	Prothrombin	ApoA-I
21	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES
	CK-MB	BMP-1	CNDP1	GAPDH, liver	Catalase	ApoA-I
22	IL-17B	CadherinE	ERBB1	METAP1	CK-MB	RGM-C
	GAPDH, liver	MMP-7	IGFBP-2	NACA	ApoA-I	MK13
23	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	GAPDH, liver	b-ECGF	BMP-1	MEK1	MMR	IGFBP-2
24	CK-MB	MMR	GAPDH, liver	CadherinE	RGM-C	METAP1
	YES	ERBB1	b-ECGF	Catalase	ApoA-I	BMP-1
25	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C
	GAPDH, liver	b-ECGF	IGFBP-2	NACA	CNDP1	LRIG3
26	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	b-ECGF	MMR	GAPDH, liver	BMP-1	ApoA-I
27	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES
	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	BLC
28	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	MMP-7	GAPDH, liver	CNDP1	b-ECGF	NACA	BMP-1
29	CSK	KPCI	ERBB1	CadherinE	RGM-C	MMR
	b-ECGF	CalpainI	ApoA-I	BMP-1	YES	GAPDH, liver
30	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	GAPDH, liver	Catalase	IGFBP-2	BMP-1	ApoA-I	VEGF
31	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	CathepsinH	b-ECGF	IGFBP-2	Catalase	MEK1
32	CadherinE	IGFBP-2	METAP1	ERBB1	MK13	CK-MB
	RGM-C	NACA	YES	CNDP1	HSP90a	ApoA-I
33	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES
	CK-MB	HSP90a	MMP-7	GAPDH, liver	CNDP1	ApoA-I
34	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	GAPDH, liver	b-ECGF	BMP-1	IL-17B	CalpainI	ApoA-I
35	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	MMR	SCFsR	BMP-1	MK13	IMB1	FGF-17
36	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C
	GAPDH, liver	MMR	Catalase	ApoA-I	MEK1	C9
37	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	KPCI	MMR	MK13	Prothrombin	NAGK	MEK1
38	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C
	GAPDH, liver	NACA	CNDP1	MK13	MEK1	LRIG3
39	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES
	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	HMG-1
40	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	MMP-7	GAPDH, liver	CathepsinH	Prothrombin	C9
41	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA
	CNDP1	b-ECGF	Prothrombin	ApoA-I	CD30Ligand	NAGK
42	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	b-ECGF	MMR	GAPDH, liver	BMP-1	Prothrombin
43	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES
	CK-MB	HSP90a	MMP-7	GAPDH, liver	CNDP1	ApoA-I
44	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	GAPDH, liver	b-ECGF	BMP-1	IL-17B	IMB1	ApoA-I
45	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C
	b-ECGF	CalpainI	MMR	BMP-1	GAPDH, liver	IGFBP-2
46	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA
	CNDP1	b-ECGF	Catalase	ApoA-I	IGFBP-2	RGM-C
47	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES
	FGF-17	RGM-C	CNDP1	IGFBP-2	Catalase	GAPDH, liver
48	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	MMR	b-ECGF	SCFsR	IMB1	BMP-1	CalpainI
49	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	GAPDH, liver	b-ECGF	CalpainI	BMP-1	CD30Ligand	ApoA-I
50	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	GAPDH, liver	b-ECGF	CalpainI	BMP-1	C9	MMR
51	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	MMP-7	NAGK	Catalase	Prothrombin	CathepsinH
52	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	GAPDH, liver	Catalase	IGFBP-2	BMP-1	ApoA-I	HMG-1
53	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR
	YES	ERBB1	RGM-C	BMP-1	CalpainI	b-ECGF
54	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C
	b-ECGF	CalpainI	MMR	BMP-1	GAPDH, liver	IL-17B
55	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA
	CNDP1	b-ECGF	Catalase	ApoA-I	IGFBP-2	RGM-C
56	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES
	BMP-1	SCFsR	CNDP1	VEGF	CalpainI	MK13
57	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	GAPDH, liver	b-ECGF	IGFBP-2	C9	Catalase	ApoA-I
58	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA
	CNDP1	b-ECGF	Catalase	ApoA-I	IGFBP-2	RGM-C

TABLE 14-continued

59	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C
	GAPDH, liver	b-ECGF	IGFBP-2	NACA	CNDP1	ApoA-I
60	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB
	YES	CNDP1	IGFBP-2	Prothrombin	NACA	CD30Ligand
61	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	MMR	b-ECGF	SCFsR	IMB1	BMP-1	CalpainI
62	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR
	YES	ERBB1	RGM-C	BMP-1	GAPDH, liver	FGF-17
63	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES
	BMP-1	SCFsR	KPCI	Catalase	b-ECGF	CNDP1
64	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES
	BMP-1	SCFsR	KPCI	IGFBP-2	CNDP1	HSP90a
65	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	GAPDH, liver	b-ECGF	IGFBP-2	Catalase	HSP90b	BMP-1
66	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	VEGF	IL-17B	BMP-1	GAPDH, liver	ApoA-I
67	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	GAPDH, liver	FGF-17	IGFBP-2	HSP90a	ApoA-I	C9
68	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	MMR	b-ECGF	SCFsR	IMB1	BMP-1	CalpainI
69	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	MMP-7	NAGK	b-ECGF	IGFBP-2	MEK1
70	YES	CK-MB	ERBB1	CadherinE	GAPDH, liver	VEGF
	CNDP1	MEK1	SCFsR	BMP-1	IGFBP-2	Proteinase-3
71	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB
	IGFBP-2	CNDP1	YES	KPCI	MK13	ApoA-I
72	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C
	GAPDH, liver	b-ECGF	IGFBP-2	NACA	CNDP1	FGF-17
73	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	MMR	b-ECGF	SCFsR	IMB1	BMP-1	CD30Ligand
74	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C
	GAPDH, liver	NACA	CNDP1	MK13	MEK1	LRIG3
75	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	IGFBP-2	MEK1	Catalase	ApoA-I	Prothrombin
76	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C
	GAPDH, liver	MMR	IGFBP-2	ApoA-I	BMP-1	HMG-1
77	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	GAPDH, liver	b-ECGF	IGFBP-2	Catalase	HSP90b	BMP-1
78	SCFsR	ERBB1	CadherinE	METAP1	IMB1	RGM-C
	VEGF	YES	IL-17B	BMP-1	GAPDH, liver	IGFBP-2
79	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES
	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	HMG-1
80	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C
	IGFBP-2	KPCI	MK13	CNDP1	Prothrombin	NAGK
81	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	GAPDH, liver	Catalase	MEK1	IGFBP-2	C9	Proteinase-3
82	MMR	ERBB1	GAPDH, liver	CadherinE	RGM-C	CK-MB
	FGF-17	ApoA-I	YES	b-ECGF	IGFBP-2	Prothrombin
83	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	HMG-1	KPCI	IGFBP-2	CNDP1	GAPDH, liver	MMR
84	CSK	CadherinE	CK-MB	GAPDH, liver	ERBB1	YES
	RGM-C	CNDP1	VEGF	Catalase	IGFBP-2	NACA
85	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C
	GAPDH, liver	NACA	CNDP1	MK13	BMP-1	ApoA-I
86	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	b-ECGF	BMP-1	GAPDH, liver	Catalase	CathepsinH
87	CK-MB	SCFsR	METAP1	CadherinE	ERBB1	IGFBP-2
	HSP90a	CNDP1	ApoA-I	GAPDH, liver	b-ECGF	MMP-7
88	b-ECGF	CadherinE	ERBB1	HSP90b	RGM-C	YES
	CK-MB	BMP-1	CNDP1	GAPDH, liver	Catalase	NAGK
89	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	NACA	VEGF	IL-17B	GAPDH, liver	b-ECGF	MMP-7
90	RGM-C	CK-MB	ERBB1	CSK	CadherinE	CNDP1
	GAPDH, liver	b-ECGF	CalpainI	BMP-1	C9	MMR
91	CNDP1	ERBB1	CadherinE	KPCI	SCFsR	RGM-C
	b-ECGF	CalpainI	MMR	BMP-1	GAPDH, liver	IGFBP-2
92	MMR	SCFsR	CadherinE	CalpainI	ERBB1	RGM-C
	GAPDH, liver	b-ECGF	IGFBP-2	NACA	CNDP1	FGF-17
93	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	MMP-7	GAPDH, liver	CNDP1	b-ECGF	ApoA-I	IGFBP-2
94	MMR	ERBB1	METAP1	CK-MB	CadherinE	YES
	FGF-17	IGFBP-2	CNDP1	SCFsR	MK13	NACA
95	YES	CadherinE	ERBB1	CSK	SCFsR	RGM-C
	GAPDH, liver	NACA	CNDP1	MK13	MEK1	CD30Ligand
96	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB
	IGFBP-2	CNDP1	YES	KPCI	Prothrombin	BMP-1
97	CK-MB	IGFBP-2	KPCI	CadherinE	METAP1	SCFsR
	YES	ERBB1	RGM-C	BMP-1	ApoA-I	CathepsinH
98	RGM-C	CadherinE	ERBB1	GAPDH, liver	SCFsR	CK-MB
	IGFBP-2	CNDP1	YES	HSP90a	BMP-1	VEGF

TABLE 14-continued

99	RGM-C	METAP1	SCFsR	ERBB1	YES	CadherinE
	GAPDH, liver	b-ECGF	IGFBP-2	Catalase	HSP90b	MMP-7
100	MMP-7	ERBB1	YES	METAP1	CadherinE	NACA
	CNDP1	b-ECGF	Prothrombin	ApoA-I	RGM-C	GAPDH, liver

	Biomarkers		Sensitivity	Specificity	Sens. + Spec.	AUC
1	MMP-7	SCFsR	0.93	0.805	1.734	0.914
	Catalase					
2	BMP-1	SCFsR	0.883	0.829	1.711	0.9
	BLC					
3	CK-MB	Catalase	0.93	0.798	1.727	0.912
	C9					
4	METAP1	SCFsR	0.92	0.79	1.711	0.898
	CATC					
5	MMP-7	NACA	0.92	0.805	1.725	0.9
	GAPDH, liver					
6	CK-MB	SCFsR	0.911	0.795	1.706	0.899
	Cadherin-6					
7	CK-MB	CSK	0.911	0.821	1.732	0.906
	BMP-1					
8	CK-MB	CNDP1	0.93	0.802	1.732	0.901
	Prothrombin					
9	YES	GAPDH, liver	0.93	0.8	1.73	0.907
	ApoA-I					
10	CK-MB	CNDP1	0.934	0.798	1.732	0.9
	NAGK					
11	CK-MB	CSK	0.925	0.805	1.73	0.899
	IL-17B					
12	BMP-1	SCFsR	0.897	0.819	1.716	0.907
	LGMN					
13	YES	GAPDH, liver	0.915	0.814	1.73	0.904
	MEK1					
14	CK-MB	CNDP1	0.915	0.81	1.725	0.904
	Proteinase-3					
15	METAP1	C9	0.906	0.805	1.711	0.899
	BLC					
16	CK-MB	CNDP1	0.925	0.786	1.711	0.895
	CATC					
17	CK-MB	CNDP1	0.911	0.795	1.706	0.899
	Cadherin-6					
18	CK-MB	CNDP1	0.93	0.795	1.725	0.902
	ApoA-I					
19	BMP-1	SCFsR	0.906	0.819	1.725	0.91
	HMG-1					
20	CK-MB	SCFsR	0.92	0.802	1.723	0.905
	HSP90a					
21	METAP1	SCFsR	0.92	0.802	1.723	0.908
	IGFBP-2					
22	YES	SCFsR	0.93	0.798	1.727	0.901
	MEK1					
23	CK-MB	CNDP1	0.92	0.807	1.727	0.906
	IMB1					
24	IGFBP-2	SCFsR	0.915	0.798	1.713	0.907
	LGMN					
25	CK-MB	CSK	0.92	0.807	1.727	0.901
	MEK1					
26	CK-MB	CNDP1	0.915	0.805	1.72	0.905
	Proteinase-3					
27	BMP-1	SCFsR	0.892	0.817	1.709	0.903
	HMG-1					
28	CK-MB	Catalase	0.925	0.783	1.708	0.899
	CATC					
29	CNDP1	SCFsR	0.92	0.805	1.725	0.897
	CD30Ligand					
30	YES	SCFsR	0.883	0.819	1.702	0.903
	Cadherin-6					
31	CK-MB	CNDP1	0.925	0.798	1.723	0.901
	GAPDH, liver					
32	SCFsR	MEK1	0.92	0.802	1.723	0.902
	Prothrombin					
33	METAP1	SCFsR	0.915	0.805	1.72	0.905
	LRIG3					
34	CK-MB	CNDP1	0.911	0.814	1.725	0.904
	VEGF					
35	YES	GAPDH, liver	0.915	0.81	1.725	0.907
	Prothrombin					
36	IGFBP-2	CK-MB	0.897	0.814	1.711	0.903
	LGMN					

TABLE 14-continued

37	CK-MB IGFBP-2	CNDP1	0.92	0.81	1.73	0.901
38	CK-MB Proteinase-3	MMR	0.901	0.817	1.718	0.902
39	BMP-1 BLC	SCFsR	0.892	0.817	1.709	0.903
40	CK-MB CATC	CNDP1	0.925	0.783	1.708	0.898
41	CK-MB RGM-C	SCFsR	0.93	0.795	1.725	0.902
42	CK-MB Cadherin-6	CNDP1	0.911	0.79	1.701	0.896
43	METAP1 CSK	SCFsR	0.915	0.805	1.72	0.9
44	CK-MB VEGF	CNDP1	0.92	0.805	1.725	0.902
45	CK-MB LGMN	CSK	0.906	0.805	1.711	0.898
46	CK-MB Proteinase-3	SCFsR	0.915	0.802	1.718	0.906
47	SCFsR BLC	KPCI	0.915	0.793	1.708	0.897
48	YES CATC	GAPDH, liver	0.911	0.795	1.706	0.896
49	YES VEGF	SCFsR	0.906	0.817	1.723	0.907
50	YES Cadherin-6	SCFsR	0.892	0.807	1.699	0.9
51	CK-MB ApoA-I	CNDP1	0.925	0.798	1.723	0.903
52	YES VEGF	SCFsR	0.915	0.81	1.725	0.914
53	CNDP1 HSP90b	Catalase	0.906	0.812	1.718	0.895
54	CK-MB IGFBP-2	CSK	0.911	0.812	1.723	0.9
55	CK-MB LGMN	SCFsR	0.92	0.79	1.711	0.903
56	RGM-C LRIG3	GAPDH, liver	0.911	0.812	1.723	0.908
57	CK-MB Proteinase-3	CNDP1	0.915	0.802	1.718	0.909
58	CK-MB BLC	SCFsR	0.92	0.788	1.708	0.9
59	CK-MB CATC	CSK	0.915	0.79	1.706	0.897
60	CSK MMP-7	MEK1	0.911	0.812	1.723	0.905
61	YES Cadherin-6	GAPDH, liver	0.897	0.802	1.699	0.896
62	CNDP1 CathepsinH	Catalase	0.925	0.798	1.723	0.902
63	RGM-C HMG-1	GAPDH, liver	0.92	0.805	1.725	0.901
64	RGM-C IMB1	GAPDH, liver	0.92	0.802	1.723	0.896
65	CK-MB CalpainI	CNDP1	0.911	0.807	1.718	0.901
66	CK-MB b-ECGF	CNDP1	0.92	0.802	1.723	0.901
67	YES LGMN	SCFsR	0.892	0.817	1.709	0.905
68	YES LRIG3	GAPDH, liver	0.911	0.812	1.723	0.903
69	CK-MB Prothrombin	CNDP1	0.925	0.802	1.727	0.902
70	RGM-C MK13	CSK	0.883	0.833	1.716	0.904
71	CSK BLC	MMR	0.897	0.81	1.706	0.9
72	CK-MB CATC	CSK	0.915	0.79	1.706	0.895
73	YES ApoA-I	GAPDH, liver	0.92	0.802	1.723	0.907
74	CK-MB Cadherin-6	MMR	0.883	0.814	1.697	0.896
75	CK-MB CathepsinH	CNDP1	0.925	0.798	1.723	0.903
76	CK-MB CNDP1	VEGF	0.897	0.826	1.723	0.914

TABLE 14-continued

77	CK-MB MEK1	CNDP1	0.911	0.807	1.718	0.905
78	CNDP1 ApoA-I	CK-MB	0.915	0.805	1.72	0.905
79	BMP-1 LGMN	SCFsR	0.892	0.817	1.709	0.904
80	CK-MB ApoA-I	CSK	0.911	0.814	1.725	0.902
81	YES ApoA-I	SCFsR	0.897	0.819	1.716	0.908
82	METAP1 BLC	SCFsR	0.901	0.805	1.706	0.902
83	CK-MB CATC	BMP-1	0.915	0.79	1.706	0.896
84	BMP-1 CD30Ligand	SCFsR	0.92	0.802	1.723	0.905
85	CK-MB Cadherin-6	MMR	0.892	0.805	1.697	0.899
86	CK-MB VEGF	CNDP1	0.925	0.798	1.723	0.902
87	YES Prothrombin	RGM-C	0.93	0.793	1.722	0.911
88	METAP1 VEGF	SCFsR	0.915	0.802	1.718	0.902
89	CK-MB HMG-1	CNDP1	0.915	0.805	1.72	0.899
90	YES LGMN	SCFsR	0.897	0.812	1.709	0.904
91	CK-MB LRIG3	CSK	0.911	0.812	1.723	0.902
92	CK-MB Proteinase-3	CSK	0.901	0.814	1.716	0.9
93	CK-MB BLC	Catalase	0.901	0.805	1.706	0.907
94	RGM-C CATC	GAPDH, liver	0.911	0.793	1.704	0.898
95	CK-MB IGFBP-2	MMR	0.906	0.814	1.72	0.905
96	CSK Cadherin-6	MMR	0.897	0.8	1.697	0.898
97	CNDP1 CalpainI	Catalase	0.911	0.81	1.72	0.902
98	CSK ApoA-I	MMR	0.897	0.824	1.721	0.911
99	CK-MB HMG-1	CNDP1	0.92	0.798	1.718	0.906
100	CK-MB IL-17B	SCFsR	0.92	0.8	1.72	0.902

Marker	Count	Marker	Count
SCFsR	100	CalpainI	22
RGM-C	100	MEK1	17
ERBB1	100	KPCI	17
CadherinE	100	MK13	15
CK-MB	99	HMG-1	11
CNDP1	95	FGF-17	11
YES	90	IMB1	10
GAPDH, liver	85	C9	10
IGFBP-2	62	IL-17B	9
b-ECGF	60	HSP90b	9
METAP1	57	HSP90a	9
BMP-1	54	CathepsinH	9
ApoA-I	46	Cadherin-6	9
MMR	44	CD30Ligand	9
CSK	44	CATC	9
NACA	39	BLC	9
Catalase	37	Proteinase-3	8
MMP-7	25	NAGK	8
Prothrombin	24	LRIG3	8
VEGF	22	LGMN	8

TABLE 15

100 Panels of 3 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers			Sensitivity	Specificity	Sens. + Spec.	AUC
1	CK-MB	C9	AMPM2	0.789	0.812	1.601	0.852
2	BLC	SCFsR	CyclophilinA	0.77	0.824	1.594	0.859
3	PTN	BMP-1	HSP90a	0.784	0.821	1.605	0.875
4	BTK	Kallikrein7	ERBB1	0.803	0.821	1.624	0.862
5	C1s	CyclophilinA	ERBB1	0.789	0.798	1.587	0.862
6	CD30Ligand	GAPDH, liver	ERBB1	0.779	0.83	1.609	0.87
7	CDK5-p35	HSP90a	ERBB1	0.793	0.804	1.597	0.876
8	PTN	CNDP1	HSP90a	0.77	0.835	1.605	0.876
9	Kallikrein7	CSK	ERBB1	0.808	0.804	1.611	0.862
10	Contactin-5	PTN	HSP90a	0.789	0.801	1.59	0.869
11	sL-Selectin	Endostatin	HSP90a	0.798	0.81	1.608	0.851
12	FGF-17	HSP90a	ERBB1	0.798	0.804	1.602	0.868
13	FYN	PTN	HSP90a	0.812	0.79	1.602	0.853
14	IGFBP-2	ERBB1	RAC1	0.779	0.841	1.62	0.875
15	IL-15Ra	PTN	HSP90a	0.793	0.812	1.606	0.866
16	CK-MB	ERBB1	KPCI	0.803	0.81	1.612	0.853
17	LDH-H1	PTN	HSP90a	0.793	0.807	1.6	0.853
18	PTN	LRIG3	HSP90a	0.798	0.83	1.628	0.88
19	MEK1	PTN	HSP90a	0.775	0.804	1.579	0.847
20	MIP-5	GAPDH, liver	ERBB1	0.784	0.804	1.588	0.855
21	Midkine	PTN	HSP90a	0.793	0.793	1.586	0.858
22	CK-MB	PARC	HSP90a	0.812	0.815	1.628	0.864
23	Prothrombin	PTN	HSP90a	0.836	0.801	1.637	0.865
24	Renin	PTN	HSP90a	0.779	0.812	1.592	0.866
25	CK-MB	TCTP	ERBB1	0.817	0.793	1.61	0.869
26	UBE2N	PTN	IGFBP-2	0.793	0.807	1.6	0.867
27	Ubiquitin + 1	PTN	CD30Ligand	0.845	0.744	1.589	0.852
28	Kallikrein7	BMP-1	AMPM2	0.775	0.818	1.593	0.835
29	BLC	C9	AMPM2	0.756	0.818	1.574	0.849
30	BTK	IGFBP-2	ERBB1	0.77	0.827	1.597	0.863
31	C1s	UBE2N	PTN	0.798	0.776	1.574	0.864
32	CDK5-p35	KPCI	ERBB1	0.779	0.815	1.595	0.86
33	CNDP1	SCFsR	HSP90a	0.784	0.81	1.594	0.853
34	CK-MB	ERBB1	CSK	0.808	0.795	1.603	0.87
35	Contactin-5	CK-MB	AMPM2	0.746	0.83	1.576	0.84
36	Endostatin	PTN	HSP90a	0.779	0.821	1.6	0.872
37	FGF-17	PTN	HSP90a	0.812	0.79	1.602	0.861
38	IL-15Ra	PTN	RAC1	0.817	0.787	1.604	0.858
39	LDH-H1	BTK	ERBB1	0.784	0.807	1.591	0.857
40	CK-MB	LRIG3	HSP90a	0.817	0.81	1.627	0.865
41	MEK1	Kallikrein7	ERBB1	0.751	0.824	1.575	0.84
42	PTN	GAPDH, liver	MIP-5	0.784	0.798	1.582	0.857
43	PARC	RAC1	ERBB1	0.793	0.827	1.62	0.867
44	Prothrombin	Endostatin	HSP90a	0.808	0.784	1.592	0.854
45	Kallikrein7	TCTP	ERBB1	0.822	0.787	1.609	0.862
46	Ubiquitin + 1	PTN	IGFBP-2	0.784	0.787	1.571	0.856
47	sL-Selectin	PTN	HSP90a	0.798	0.801	1.599	0.87
48	TCTP	BMP-1	ERBB1	0.803	0.795	1.598	0.862
49	C1s	RAC1	PTN	0.808	0.764	1.572	0.859
50	C9	ERBB1	CyclophilinA	0.798	0.818	1.616	0.872
51	PTN	GAPDH, liver	CD30Ligand	0.803	0.801	1.604	0.861
52	CDK5-p35	PTN	HSP90a	0.793	0.801	1.595	0.863
53	CNDP1	SCFsR	KPCI	0.789	0.804	1.593	0.854
54	CSK	IGFBP-2	PTN	0.784	0.812	1.597	0.856
55	FGF-17	GAPDH, liver	ERBB1	0.775	0.815	1.59	0.864
56	CK-MB	IL-15Ra	RAC1	0.793	0.798	1.592	0.85
57	LDH-H1	CSK	ERBB1	0.789	0.793	1.581	0.856
58	LRIG3	SCFsR	HSP90a	0.808	0.787	1.594	0.863
59	MEK1	RAC1	ERBB1	0.77	0.804	1.574	0.86
60	MIP-5	UBE2N	PTN	0.793	0.784	1.578	0.855
61	PARC	CyclophilinA	ERBB1	0.775	0.821	1.596	0.869
62	Prothrombin	ERBB1	HSP90a	0.784	0.798	1.582	0.87
63	sL-Selectin	CyclophilinA	ERBB1	0.789	0.798	1.587	0.865
64	SCFsR	BMP-1	HSP90a	0.789	0.807	1.596	0.855
65	BTK	CK-MB	ERBB1	0.765	0.827	1.592	0.867
66	C9	ERBB1	RAC1	0.779	0.821	1.6	0.869
67	CD30Ligand	CyclophilinA	ERBB1	0.789	0.798	1.587	0.866
68	CDK5-p35	RAC1	ERBB1	0.803	0.79	1.593	0.87
69	CNDP1	ERBB1	HSP90a	0.77	0.812	1.582	0.862
70	CK-MB	Endostatin	HSP90a	0.789	0.807	1.596	0.856
71	FGF-17	RAC1	ERBB1	0.789	0.798	1.587	0.868
72	BTK	IL-15Ra	PTN	0.793	0.795	1.589	0.858
73	SCFsR	ERBB1	KPCI	0.789	0.815	1.604	0.862
74	LDH-H1	LRIG3	ERBB1	0.765	0.815	1.581	0.849
75	MIP-5	RAC1	ERBB1	0.775	0.801	1.576	0.865

TABLE 15-continued

76	PARC	RAC1	BMP-1	0.765	0.83	1.595	0.867
77	Prothrombin	BMP-1	HSP90a	0.789	0.793	1.581	0.85
78	PTN	ERBB1	TCTP	0.798	0.793	1.591	0.871
79	UBE2N	IGFBP-2	ERBB1	0.77	0.83	1.599	0.872
80	sL-Selectin	RAC1	ERBB1	0.779	0.804	1.583	0.862
81	PTN	IGFBP-2	AMPM2	0.775	0.818	1.593	0.856
82	SCFsR	C9	KPCI	0.789	0.81	1.598	0.861
83	CD30Ligand	KPCI	ERBB1	0.765	0.818	1.583	0.867
84	CDK5-p35	BTK	ERBB1	0.793	0.79	1.583	0.862
85	CK-MB	CNDP1	AMPM2	0.765	0.81	1.575	0.842
86	CK-MB	C9	CSK	0.793	0.801	1.595	0.857
87	Endostatin	LRIG3	HSP90a	0.798	0.793	1.591	0.859
88	FGF-17	Endostatin	HSP90a	0.793	0.793	1.586	0.853
89	PTN	LRIG3	IL-15Ra	0.775	0.81	1.584	0.848
90	LDH-H1	CyclophilinA	ERBB1	0.775	0.804	1.579	0.858
91	MIP-5	RAC1	PTN	0.817	0.759	1.575	0.866
92	PARC	CSK	ERBB1	0.775	0.818	1.593	0.862
93	Prothrombin	CyclophilinA	ERBB1	0.817	0.764	1.581	0.851
94	IGFBP-2	TCTP	PTN	0.803	0.787	1.59	0.858
95	UBE2N	PTN	ERBB1	0.765	0.824	1.589	0.87
96	sL-Selectin	BMP-1	AMPM2	0.761	0.821	1.582	0.847
97	CD30Ligand	PARC	GAPDH, liver	0.742	0.841	1.583	0.846
98	CDK5-p35	AMPM2	ERBB1	0.756	0.824	1.58	0.864
99	CNDP1	BMP-1	KPCI	0.77	0.804	1.574	0.848
100	FGF-17	UBE2N	ERBB1	0.775	0.807	1.581	0.865

Marker	Count	Marker	Count
ERBB1	45	CD30Ligand	6
PTN	32	C9	6
HSP90a	30	BTK	6
RAC1	13	sL-Selectin	5
CK-MB	12	TCTP	5
IGFBP-2	8	Prothrornbin	5
CyclophilinA	8	MIP-5	5
BMP-1	8	LDH-H1	5
AMPM2	8	Kallikrein7	5
SCFsR	7	IL-15Ra	5
KIPCI	7	MEK1	3
UBE2N	6	C1s	3
PARC	6	Ubiquitin + 1	2
LRIG3	6	Contactin-5	2
GAPDH, liver	6	BLC	2
FGF-17	6	Renin	1
Endostatin	6	Midkine	1
CSK	6	FYN	1
CNDP1	6		
CDK5-p35	6		

TABLE 16

100 Panels of 4 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers				Sensitivity	Specificity	Sens. + Spec.	AUC
1	Kallikrein7	SCFsR	AMPM2	C9	0.826	0.827	1.653	0.874
2	CK-MB	BLC	CSK	ERBB1	0.822	0.824	1.645	0.87
3	CNDP1	BMP-1	RAC1	PTN	0.822	0.835	1.657	0.886
4	BTK	KPCI	ERBB1	CK-MB	0.822	0.827	1.648	0.872
5	IGFBP-2	SCFsR	RAC1	C1s	0.812	0.844	1.656	0.886
6	CD30Ligand	IGFBP-2	PTN	GAPDH, liver	0.826	0.827	1.653	0.885
7	CDK5-p35	SCFsR	HSP90a	ERBB1	0.817	0.844	1.661	0.889
8	Contactin-5	CSK	CK-MB	ERBB1	0.812	0.832	1.645	0.871
9	IGFBP-2	CyclophilinA	ERBB1	Kallikrein7	0.826	0.832	1.659	0.882
10	FGF-17	Kallikrein7	HSP90a	Endostatin	0.822	0.824	1.645	0.871
11	CK-MB	PARC	HSP90a	FYN	0.822	0.807	1.628	0.864
12	IL-15Ra	CyclophilinA	C9	SCFsR	0.812	0.835	1.647	0.881
13	LDH-H1	PTN	ERBB1	HSP90a	0.793	0.852	1.646	0.882
14	LRIG3	SCFsR	HSP90a	PTN	0.84	0.835	1.676	0.896
15	LDH-H1	Kallikrein7	ERBB1	MEK1	0.817	0.815	1.632	0.857
16	MIP-5	PTN	ERBB1	RAC1	0.817	0.83	1.646	0.89
17	Midkine	PTN	HSP90a	IGFBP-2	0.798	0.838	1.636	0.877
18	PTN	CNDP1	HSP90a	Prothrombin	0.826	0.827	1.653	0.88
19	Renin	Kallikrein7	HSP90a	LRIG3	0.84	0.81	1.65	0.866
20	CK-MB	PARC	TCTP	ERBB1	0.812	0.83	1.642	0.882
21	UBE2N	Kallikrein7	ERBB1	IGFBP-2	0.812	0.838	1.65	0.883
22	Ubiquitin + 1	BTK	ERBB1	PARC	0.803	0.818	1.621	0.874

TABLE 16-continued

23	sL-Selectin	CyclophilinA	ERBB1	PTN	0.817	0.835	1.652	0.879
24	LRIG3	IGFBP-2	AMPM2	SCFsR	0.831	0.821	1.652	0.873
25	BLC	C9	CyclophilinA	SCFsR	0.793	0.849	1.643	0.882
26	PARC	BMP-1	CSK	Kallikrein7	0.808	0.841	1.648	0.866
27	C1s	IGFBP-2	PTN	RAC1	0.822	0.818	1.64	0.894
28	CD30Ligand	SCFsR	RAC1	C9	0.822	0.83	1.651	0.887
29	CDK5-p35	Kallikrein7	HSP90a	ERBB1	0.831	0.818	1.649	0.885
30	Contactin-5	CyclophilinA	ERBB1	CK-MB	0.789	0.849	1.638	0.874
31	Endostatin	GAPDH, liver	HSP90a	CK-MB	0.817	0.824	1.641	0.866
32	FGF-17	SCFsR	ERBB1	CyclophilinA	0.803	0.838	1.641	0.888
33	FYN	GAPDH, liver	ERBB1	CD30Ligand	0.798	0.827	1.625	0.871
34	IL-15Ra	sL-Selectin	HSP90a	PTN	0.803	0.838	1.641	0.876
35	BTK	KPCI	SCFsR	ERBB1	0.826	0.821	1.647	0.877
36	MEK1	HSP90a	ERBB1	PTN	0.77	0.855	1.625	0.875
37	MIP-5	KPCI	PTN	Kallikrein7	0.826	0.818	1.644	0.86
38	Midkine	CyclophilinA	ERBB1	Kallikrein7	0.817	0.807	1.624	0.869
39	Prothrombin	IGFBP-2	HSP90a	PTN	0.822	0.821	1.643	0.887
40	PARC	PTN	HSP90a	Renin	0.817	0.821	1.638	0.879
41	BLC	ERBB1	TCTP	CK-MB	0.822	0.818	1.64	0.87
42	PTN	SCFsR	UBE2N	IGFBP-2	0.817	0.83	1.646	0.89
43	CDK5-p35	Ubiquitin + 1	ERBB1	IGFBP-2	0.793	0.827	1.62	0.879
44	sL-Selectin	IGFBP-2	AMPM2	PTN	0.826	0.818	1.644	0.865
45	BMP-1	ERBB1	RAC1	Kallikrein7	0.812	0.832	1.645	0.878
46	C1s	C9	CyclophilinA	SCFsR	0.822	0.815	1.637	0.878
47	Kallikrein7	CNDP1	HSP90a	ERBB1	0.812	0.841	1.653	0.872
48	Contactin-5	CK-MB	HSP90a	GAPDH, liver	0.812	0.824	1.636	0.86
49	Endostatin	Kallikrein7	HSP90a	CK-MB	0.822	0.815	1.637	0.874
50	FGF-17	Kallikrein7	HSP90a	ERBB1	0.826	0.81	1.636	0.881
51	FYN	CK-MB	ERBB1	KPCI	0.808	0.815	1.623	0.857
52	IL-15Ra	CyclophilinA	PTN	ERBB1	0.793	0.841	1.634	0.885
53	LDH-H1	PTN	ERBB1	BTK	0.808	0.835	1.643	0.878
54	MEK1	HSP90a	ERBB1	Kallikrein7	0.803	0.818	1.621	0.864
55	PTN	GAPDH, liver	IGFBP-2	MIP-5	0.817	0.824	1.641	0.875
56	Midkine	ERBB1	HSP90a	PTN	0.77	0.852	1.622	0.886
57	Prothrombin	LRIG3	HSP90a	PTN	0.826	0.815	1.642	0.881
58	Renin	Kallikrein7	HSP90a	PTN	0.803	0.83	1.632	0.879
59	PTN	ERBB1	TCTP	Kallikrein7	0.812	0.827	1.639	0.881
60	PTN	ERBB1	IGFBP-2	UBE2N	0.793	0.849	1.643	0.887
61	Ubiquitin + 1	PTN	IGFBP-2	sL-Selectin	0.779	0.838	1.617	0.861
62	CDK5-p35	SCFsR	AMPM2	IGFBP-2	0.803	0.835	1.638	0.875
63	BLC	SCFsR	KPCI	IGFBP-2	0.812	0.815	1.628	0.871
64	BMP-1	ERBB1	RAC1	CDK5-p35	0.812	0.832	1.645	0.884
65	C1s	PTN	ERBB1	HSP90a	0.784	0.852	1.636	0.887
66	CD30Ligand	Kallikrein7	RAC1	ERBB1	0.836	0.812	1.648	0.886
67	Kallikrein7	CNDP1	HSP90a	PTN	0.798	0.852	1.65	0.885
68	CK-MB	PARC	CSK	ERBB1	0.817	0.827	1.644	0.884
69	Contactin-5	BTK	ERBB1	CK-MB	0.775	0.861	1.635	0.868
70	Endostatin	Kallikrein7	RAC1	CD30Ligand	0.836	0.801	1.637	0.873
71	FGF-17	SCFsR	ERBB1	UBE2N	0.793	0.841	1.634	0.886
72	FYN	KPCI	ERBB1	C9	0.808	0.815	1.623	0.861
73	IL-15Ra	CSK	PTN	IGFBP-2	0.808	0.827	1.634	0.87
74	LDH-H1	PTN	ERBB1	CyclophilinA	0.812	0.827	1.639	0.876
75	PTN	GAPDH, liver	IGFBP-2	MEK1	0.793	0.824	1.617	0.861
76	MIP-5	UBE2N	ERBB1	PTN	0.784	0.847	1.631	0.883
77	Midkine	SCFsR	HSP90a	PTN	0.798	0.824	1.622	0.877
78	Prothrombin	CK-MB	HSP90a	PARC	0.831	0.81	1.641	0.881
79	Renin	PTN	HSP90a	GAPDH, liver	0.826	0.804	1.63	0.869
80	GAPDH, liver	TCTP	ERBB1	IGFBP-2	0.817	0.818	1.635	0.872
81	Ubiquitin + 1	BTK	ERBB1	IGFBP-2	0.812	0.804	1.616	0.875
82	PTN	SCFsR	AMPM2	IGFBP-2	0.803	0.832	1.635	0.879
83	BLC	SCFsR	TCTP	ERBB1	0.817	0.81	1.627	0.873
84	CDK5-p35	SCFsR	HSP90a	BMP-1	0.817	0.824	1.641	0.872
85	C1s	Kallikrein7	ERBB1	CyclophilinA	0.817	0.818	1.635	0.875
86	sL-Selectin	CNDP1	HSP90a	PTN	0.798	0.844	1.642	0.881
87	IGFBP-2	ERBB1	RAC1	Contactin-5	0.779	0.852	1.632	0.879
88	Endostatin	LRIG3	HSP90a	PTN	0.798	0.838	1.636	0.892
89	FGF-17	Endostatin	HSP90a	Prothrombin	0.831	0.801	1.632	0.865
90	Kallikrein7	ERBB1	HSP90a	FYN	0.808	0.812	1.62	0.872
91	IL-15Ra	LRIG3	HSP90a	PTN	0.798	0.835	1.633	0.886
92	SCFsR	ERBB1	LDH-H1	HSP90a	0.789	0.847	1.635	0.869
93	MEK1	CyclophilinA	ERBB1	PTN	0.798	0.818	1.616	0.866
94	BTK	ERBB1	MIP-5	PTN	0.789	0.841	1.63	0.879
95	Midkine	RAC1	ERBB1	PARC	0.798	0.821	1.619	0.866
96	IGFBP-2	HSP90a	Renin	PTN	0.793	0.835	1.629	0.885
97	PTN	ERBB1	IGFBP-2	Ubiquitin + 1	0.765	0.849	1.615	0.876
98	PTN	LRIG3	AMPM2	CD30Ligand	0.798	0.835	1.633	0.868
99	BLC	SCFsR	TCTP	C9	0.817	0.807	1.624	0.876
100	UBE2N	PARC	SCFsR	BMP-1	0.793	0.844	1.637	0.88

TABLE 16-continued

Marker	Count	Marker	Count
ERBB1	51	BMP-1	6
PTN	42	BLC	6
HSP90a	35	AMPM2	6
IGFBP-2	24	sL-Selectin	5
SCFsR	22	Ubiquitin + 1	5
Kallikrein7	22	Renin	5
CK-MB	14	Prothrombin	5
CyclophilinA	12	Midkine	5
RAC1	11	MIP-5	5
PARC	9	MEK1	5
GAPDH, liver	8	LDH-H1	5
LRIG3	7	IL-15Ra	5
C9	7	FYN	5
BTK	7	FGF-17	5
UBE2N	6	Contactin-5	5
TCTP	6	CSK	5
KPCI	6	CNDP1	5
Endostatin	6	C1s	5
CDK5-p35	6		
CD30Ligand	6		

TABLE 17

100 Panels of 5 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers					Sensitivity	Specificity	Sens. + Spec.	AUC
1	CD30Ligand	IGFBP-2	PTN	sL-Selectin	AMPM2	0.845	0.83	1.675	0.883
2	KPCI	TCTP	ERBB1	CK-MB	BLC	0.84	0.821	1.661	0.877
3	CNDP1	BMP-1	RAC1	PTN	LRIG3	0.826	0.855	1.681	0.891
4	IGFBP-2	SCFsR	GAPDH, liver	PTN	BTK	0.854	0.838	1.693	0.899
5	UBE2N	IGFBP-2	SCFsR	C1s	PTN	0.822	0.861	1.682	0.906
6	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	C9	0.845	0.838	1.683	0.889
7	CDK5-p35	KPCI	ERBB1	HSP90a	SCFsR	0.84	0.841	1.681	0.886
8	PARC	CSK	ERBB1	Kallikrein7	CK-MB	0.836	0.852	1.688	0.897
9	Contactin-5	CSK	ERBB1	PARC	CK-MB	0.812	0.861	1.673	0.882
10	Endostatin	LRIG3	HSP90a	CK-MB	PTN	0.812	0.872	1.684	0.903
11	IGFBP-2	SCFsR	RAC1	ERBB1	FGF-17	0.812	0.866	1.679	0.9
12	Kallikrein7	RAC1	IGFBP-2	ERBB1	FYN	0.84	0.83	1.67	0.886
13	Prothrombin	PTN	HSP90a	IL-15Ra	sL-Selectin	0.85	0.827	1.676	0.887
14	LDH-H1	CK-MB	ERBB1	CyclophilinA	Kallikrein7	0.85	0.835	1.685	0.888
15	MEK1	HSP90a	ERBB1	Kallikrein7	PTN	0.817	0.849	1.666	0.887
16	MIP-5	SCFsR	RAC1	C9	PTN	0.826	0.847	1.673	0.898
17	Midkine	ERBB1	HSP90a	Kallikrein7	CK-MB	0.817	0.852	1.669	0.886
18	CK-MB	Kallikrein7	HSP90a	LRIG3	Renin	0.84	0.827	1.667	0.885
19	CD30Ligand	IGFBP-2	PTN	sL-Selectin	Ubiquitin + 1	0.84	0.849	1.69	0.889
20	CSK	AMPM2	IGFBP-2	ERBB1	Kallikrein7	0.84	0.832	1.673	0.876
21	BLC	SCFsR	CSK	ERBB1	KPCI	0.84	0.818	1.659	0.883
22	KPCI	HSP90a	PTN	Kallikrein7	BMP-1	0.836	0.835	1.671	0.875
23	BTK	HSP90a	ERBB1	PTN	SCFsR	0.84	0.844	1.684	0.902
24	C1s	PTN	ERBB1	UBF2N	LDH-H1	0.826	0.855	1.681	0.891
25	CDK5-p35	CK-MB	HSP90a	ERBB1	Kallikrein7	0.831	0.849	1.68	0.898
26	Kallikrein7	LRIG3	HSP90a	PTN	CNDP1	0.826	0.852	1.679	0.893
27	Contactin-5	CK-MB	HSP90a	LRIG3	PTN	0.808	0.861	1.668	0.9
28	SCFsR	C9	CSK	Kallikrein7	Endostatin	0.859	0.821	1.68	0.89
29	PTN	ERBB1	IGFBP-2	UBE2N	FGF-17	0.822	0.852	1.674	0.892
30	Kallikrein7	ERBB1	HSP90a	FYN	CK-MB	0.831	0.835	1.666	0.889
31	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand	0.836	0.852	1.688	0.906
32	IL-15Ra	CyclophilinA	ERBB1	Kallikrein7	CK-MB	0.808	0.866	1.674	0.887
33	PARC	GAPDH, liver	SCFsR	BMP-1	MEK1	0.803	0.858	1.661	0.875
34	PTN	RAC1	IGFBP-2	PARC	MIP-5	0.817	0.855	1.672	0.894
35	Midkine	SCFsR	HSP90a	PTN	LRIG3	0.831	0.838	1.669	0.893
36	Prothrombin	CK-MB	HSP90a	LRIG3	PTN	0.845	0.844	1.689	0.9
37	Renin	PTN	HSP90a	ERBB1	BTK	0.831	0.835	1.666	0.891
38	IGFBP-2	TCTP	SCFsR	ERBB1	Kallikrein7	0.845	0.827	1.672	0.891
39	LRIG3	SCFsR	HSP90a	PTN	Ubiquitin + 1	0.854	0.81	1.664	0.894
40	CK-MB	AMPM2	ERBB1	BTK	CDK5-p35	0.84	0.83	1.67	0.886
41	CDK5-p35	SCFsR	AMPM2	IGFBP-2	BLC	0.822	0.835	1.657	0.885
42	C1s	HSP90a	PTN	Kallikrein7	ERBB1	0.826	0.849	1.676	0.896
43	CNDP1	ERBB1	HSP90a	PTN	Kallikrein7	0.817	0.855	1.672	0.897
44	IGFBP-2	CyclophilinA	ERBB1	Contactin-5	Kallikrein7	0.808	0.858	1.665	0.882
45	Endostatin	Kallikrein7	CyclophilinA	ERBB1	IGFBP-2	0.822	0.852	1.674	0.88
46	SCFsR	C9	CyclophilinA	FGF-17	ERBB1	0.817	0.855	1.672	0.897
47	MIP-5	PTN	ERBB1	RAC1	FYN	0.836	0.83	1.665	0.889
48	sL-Selectin	LRIG3	HSP90a	PTN	IL-15Ra	0.831	0.841	1.672	0.894

TABLE 17-continued

49	LDH-H1	Kallikrein7	ERBB1	HSP90a	PTN	0.822	0.858	1.68	0.891
50	Kallikrein7	BMP-1	CyclophilinA	ERBB1	MEK1	0.808	0.844	1.651	0.872
51	PARC	LRIG3	HSP90a	CK-MB	Midkine	0.826	0.838	1.664	0.881
52	Prothrombin	IGFBP-2	HSP90a	ERBB1	PTN	0.822	0.858	1.68	0.898
53	IGFBP-2	HSP90a	Renin	PTN	Kallikrein7	0.822	0.844	1.665	0.896
54	CK-MB	PARC	TCTP	ERBB1	GAPDH, liver	0.831	0.838	1.669	0.886
55	CK-MB	CD30Ligand	KPCI	ERBB1	Ubiquitin + 1	0.831	0.83	1.661	0.875
56	BLC	SCFsR	CSK	ERBB1	PARC	0.822	0.832	1.654	0.879
57	PTN	SCFsR	RAC1	C1s	C9	0.817	0.858	1.675	0.902
58	CNDP1	KPCI	ERBB1	CK-MB	HSP90a	0.845	0.827	1.672	0.878
59	Kallikrein7	PTN	HSP90a	C9	Contactin-5	0.812	0.849	1.662	0.884
60	Endostatin	ERBB1	CSK	Kallikrein7	SCFsR	0.85	0.824	1.674	0.887
61	FGF-17	SCFsR	HSP90a	PTN	ERBB1	0.817	0.855	1.672	0.903
62	FYN	PTN	HSP90a	ERBB1	SCFsR	0.798	0.866	1.665	0.895
63	sL-Selectin	IGFBP-2	CyclophilinA	PTN	IL-15Ra	0.822	0.849	1.671	0.879
64	PTN	ERBB1	IGFBP-2	UBE2N	LDH-H1	0.822	0.858	1.68	0.887
65	Endostatin	Kallikrein7	CyclophilinA	ERBB1	MEK1	0.822	0.83	1.651	0.875
66	MIP-5	PTN	ERBB1	RAC1	PARC	0.817	0.855	1.672	0.892
67	CK-MB	PTN	HSP90a	LRIG3	Midkine	0.808	0.855	1.663	0.895
68	Prothrombin	CK-MB	HSP90a	Kallikrein7	ERBB1	0.826	0.847	1.673	0.897
69	CD30Ligand	Kallikrein7	KPCI	SCFsR	Renin	0.845	0.818	1.663	0.875
70	Kallikrein7	C9	ERBB1	TCTP	LDH-H1	0.845	0.824	1.669	0.881
71	Ubiquitin + 1	BTK	ERBB1	IGFBP-2	Kallikrein7	0.845	0.815	1.66	0.888
72	C9	ERBB1	AMPM2	BTK	Kallikrein7	0.822	0.847	1.668	0.88
73	CSK	KPCI	ERBB1	CK-MB	BLC	0.836	0.818	1.654	0.879
74	PTN	CNDP1	CyclophilinA	SCFsR	BMP-1	0.812	0.858	1.67	0.9
75	C1s	Kallikrein7	ERBB1	GAPDH, liver	BTK	0.85	0.824	1.674	0.881
76	IGFBP-2	SCFsR	RAC1	ERBB1	CDK5-p35	0.826	0.849	1.676	0.902
77	IGFBP-2	KPCI	CD30Ligand	PTN	Contactin-5	0.831	0.83	1.661	0.88
78	FGF-17	Kallikrein7	HSP90a	PTN	ERBB1	0.817	0.852	1.669	0.901
79	C1s	SCFsR	GAPDH, liver	C9	FYN	0.831	0.832	1.663	0.881
80	IL-15Ra	PTN	RAC1	Kallikrein7	LRIG3	0.845	0.824	1.669	0.886
81	MEK1	CyclophilinA	ERBB1	PTN	Kallikrein7	0.812	0.838	1.65	0.88
82	MIP-5	CyclophilinA	ERBB1	Kallikrein7	CK-MB	0.822	0.849	1.671	0.884
83	BTK	SCFsR	C9	Kallikrein7	Midkine	0.826	0.835	1.662	0.879
84	LRIG3	CNDP1	HSP90a	PTN	Prothrombin	0.84	0.83	1.67	0.89
85	CSK	C9	ERBB1	CK-MB	Renin	0.836	0.824	1.66	0.884
86	CD30Ligand	PTN	ERBB1	TCTP	Kallikrein7	0.84	0.827	1.667	0.895
87	PTN	SCFsR	UBE2N	IGFBP-2	LRIG3	0.822	0.855	1.677	0.901
88	CD30Ligand	SCFsR	ERBB1	CyclophilinA	Ubiquitin + 1	0.836	0.824	1.66	0.888
89	SCFsR	ERBB1	AMPM2	IGFBP-2	CDK5-p35	0.826	0.838	1.664	0.891
90	CDK5-p35	CK-MB	ERBB1	CSK	BLC	0.822	0.83	1.651	0.88
91	SCFsR	BMP-1	HSP90a	PTN	CDK5-p35	0.826	0.844	1.67	0.896
92	CK-MB	Kallikrein7	CSK	ERBB1	Contactin-5	0.822	0.838	1.66	0.883
93	Endostatin	Kallikrein7	KPCI	CD30Ligand	SCFsR	0.854	0.818	1.673	0.877
94	Kallikrein7	IGFBP-2	KPCI	SCFsR	FGF-17	0.845	0.824	1.669	0.877
95	PTN	LRIG3	HSP90a	FYN	SCFsR	0.822	0.841	1.663	0.893
96	KPCI	TCTP	ERBB1	SCFsR	IL-15Ra	0.845	0.821	1.666	0.876
97	LDH-H1	CK-MB	ERBB1	CSK	Kallikrein7	0.85	0.827	1.676	0.887
98	MEK1	HSP90a	ERBB1	Kallikrein7	C9	0.812	0.838	1.65	0.874
99	BTK	MIP-5	PTN	GAPDH, liver	ERBB1	0.826	0.841	1.667	0.894
100	sL-Selectin	PARC	HSP90a	PTN	Midkine	0.84	0.821	1.661	0.884

Marker	Count	Marker	Count
ERBB1	59	TCTP	6
PTN	48	Midkine	6
Kallikrein7	42	MIP-5	6
HSP90a	35	MEK1	6
SCFsR	34	LDH-H1	6
IGFBP-2	25	IL-15Ra	6
CK-MB	25	FYN	6
LRIG3	15	FGF-17	6
CyclophilinA	13	Endostatin	6
KPCI	12	Contactin-5	6
CSK	12	CNDP1	6
C9	12	C1s	6
RAC1	10	BMP-1	6
PARC	9	BLC	6
CD30Ligand	9	AMPM2	6
BTK	9	Ubiquitin + 1	5
CDK5-p35	8	UBE2N	5
GAPDH, liver	7	Renin	5
sL-Selectin	6	Prothrombin	5

TABLE 18

100 Panels of 6 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers						Sensitivity	Specificity	Sens. + Spec.	AUC
1	SCFsR	ERBB1	AMPM2	IGFBP-2	CDK5-p35	PARC	0.84	0.858	1.698	0.897
2	CSK	KPCI	ERBB1	CK-MB	BLC	SCFsR	0.859	0.824	1.683	0.887
3	PARC	BMP-1	CSK	ERBB1	CK-MB	GAPDH, liver	0.84	0.858	1.698	0.897
4	BTK	HSP90a	ERBB1	Kallikrein7	CK-MB	PTN	0.85	0.861	1.711	0.913
5	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2	C1s	0.869	0.838	1.707	0.883
6	CD30Ligand	SCFsR	KPCI	C9	BTK	PTN	0.869	0.835	1.704	0.898
7	LRIG3	CNDP1	HSP90a	CK-MB	PTN	Kallikrein7	0.84	0.878	1.718	0.903
8	Contactin-5	BTK	ERBB1	CK-MB	GAPDH, liver	PARC	0.817	0.878	1.695	0.895
9	LDH-H1	PTN	ERBB1	CyclophilinA	CD30Ligand	Kallikrein7	0.854	0.855	1.71	0.901
10	CD30Ligand	RAC1	PTN	sL-Selectin	Kallikrein7	Endostatin	0.859	0.844	1.703	0.898
11	LDH-H1	PTN	ERBB1	HSP90a	FGF-17	Kallikrein7	0.85	0.849	1.699	0.898
12	PTN	SCFsR	RAC1	IGFBP-2	FYN	CD30Ligand	0.873	0.835	1.708	0.908
13	CD30Ligand	KPCI	PTN	LRIG3	Kallikrein7	IL-15Ra	0.85	0.844	1.694	0.879
14	CD30Ligand	PTN	ERBB1	RAC1	Kallikrein7	MEK1	0.836	0.855	1.691	0.893
15	MIP-5	RAC1	PTN	IGFBP-2	ERBB1	LDH-H1	0.826	0.866	1.693	0.892
16	Kallikrein7	SCFsR	HSP90a	ERBB1	CDK5-p35	Midkine	0.85	0.847	1.696	0.897
17	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin	CK-MB	0.85	0.861	1.711	0.91
18	CK-MB	Kallikrein7	HSP90a	LRIG3	Renin	Prothrombin	0.864	0.827	1.691	0.891
19	IGFBP-2	TCTP	SCFsR	ERBB1	Kallikrein7	CDK5-p35	0.864	0.841	1.705	0.896
20	PTN	SCFsR	UBE2N	IGFBP-2	CD30Ligand	LDH-H1	0.85	0.861	1.711	0.903
21	CD30Ligand	SCFsR	ERBB1	CyclophilinA	Ubiquitin + 1	PTN	0.85	0.852	1.702	0.91
22	CD30Ligand	IGFBP-2	AMPM2	PTN	SCFsR	CDK5-p35	0.845	0.849	1.695	0.898
23	CSK	KPCI	ERBB1	CK-MB	BLC	Contactin-5	0.854	0.824	1.678	0.879
24	IGFBP-2	BMP-1	RAC1	PTN	SCFsR	CDK5-p35	0.831	0.864	1.695	0.906
25	C1s	PTN	ERBB1	UBE2N	Kallikrein7	LDH-H1	0.845	0.858	1.703	0.9
26	Kallikrein7	RAC1	SCFsR	C9	IGFBP-2	PARC	0.831	0.872	1.703	0.904
27	PTN	CNDP1	CyclophilinA	C1s	SCFsR	GAPDH, liver	0.864	0.838	1.702	0.906
28	Endostatin	LRIG3	HSP90a	CK-MB	PARC	Kallikrein7	0.836	0.861	1.696	0.902
29	BTK	FGF-17	ERBB1	GAPDH, liver	SCFsR	PARC	0.826	0.872	1.698	0.906
30	CK-MB	Kallikrein7	HSP90a	PARC	LRIG3	FYN	0.845	0.852	1.697	0.896
31	sL-Selectin	LRIG3	HSP90a	PTN	Prothrombin	IL-15Ra	0.859	0.832	1.692	0.9
32	Kallikrein7	RAC1	SCFsR	ERBB1	IGFBP-2	MEK1	0.845	0.841	1.686	0.896
33	Kallikrein7	IGFBP-2	KPCI	SCFsR	MIP-5	CDK5-p35	0.878	0.81	1.688	0.884
34	Midkine	CyclophilinA	ERBB1	Kallikrein7	IGFBP-2	SCFsR	0.85	0.841	1.691	0.893
35	CD30Ligand	RAC1	PTN	sL-Selectin	Kallikrein7	Renin	0.854	0.83	1.684	0.895
36	CD30Ligand	PTN	ERBB1	TCTP	IGFBP-2	Kallikrein7	0.845	0.847	1.692	0.9
37	Ubiquitin + 1	BTK	ERBB1	IGFBP-2	Kallikrein7	PARC	0.85	0.849	1.699	0.901
38	BTK	AMPM2	C9	SCFsR	Kallikrein7	FGF-17	0.85	0.841	1.691	0.89
39	CDK5-p35	CSK	ERBB1	PARC	CK-MB	BLC	0.817	0.861	1.678	0.89
40	LDH-H1	Kallikrein7	ERBB1	HSP90a	PTN	BMP-1	0.831	0.861	1.692	0.895
41	CNDP1	SCFsR	HSP90a	PTN	ERBB1	BTK	0.831	0.869	1.7	0.903
42	CK-MB	SCFsR	CSK	ERBB1	KPCI	Contactin-5	0.869	0.824	1.692	0.879
43	Endostatin	Kallikrein7	HSP90a	PTN	CK-MB	LRIG3	0.826	0.869	1.696	0.908
44	Kallikrein7	CyclophilinA	ERBB1	FYN	IGFBP-2	SCFsR	0.854	0.835	1.69	0.892
45	IGFBP-2	SCFsR	RAC1	IL-15Ra	PTN	HSP90a	0.831	0.858	1.689	0.898
46	CK-MB	SCFsR	CyclophilinA	ERBB1	KPCI	MEK1	0.85	0.832	1.682	0.874
47	CD30Ligand	KPCI	PTN	LRIG3	Kallikrein7	MIP-5	0.854	0.832	1.687	0.88
48	Midkine	ERBB1	HSP90a	Kallikrein7	CK-MB	CDK5-p35	0.836	0.852	1.688	0.898
49	Renin	LRIG3	HSP90a	PTN	Kallikrein7	IGFBP-2	0.836	0.847	1.682	0.903
50	CK-MB	Kallikrein7	HSP90a	PTN	ERBB1	TCTP	0.85	0.841	1.691	0.905
51	BTK	IGFBP-2	ERBB1	Kallikrein7	UBE2N	PARC	0.85	0.849	1.699	0.899
52	PTN	C9	CSK	CD30Ligand	SCFsR	Ubiquitin + 1	0.854	0.844	1.698	0.9
53	CK-MB	IGFBP-2	AMPM2	LRIG3	PTN	CD30Ligand	0.845	0.844	1.689	0.898
54	CK-MB	IGFBP-2	AMPM2	LRIG3	SCFsR	BLC	0.84	0.835	1.676	0.89
55	C1s	PTN	ERBB1	BTK	Kallikrein7	BMP-1	0.812	0.878	1.69	0.892
56	LRIG3	CNDP1	HSP90a	IGFBP-2	PTN	SCFsR	0.826	0.872	1.698	0.904
57	Contactin-5	CK-MB	RAC1	ERBB1	CD30Ligand	Kallikrein7	0.822	0.866	1.688	0.895
58	Endostatin	LRIG3	HSP90a	CK-MB	Kallikrein7	CDK5-p35	0.845	0.849	1.695	0.898
59	CyclophilinA	GAPDH, liver	ERBB1	PARC	SCFsR	FGF-17	0.831	0.864	1.695	0.904
60	PTN	SCFsR	RAC1	C1s	C9	FYN	0.831	0.858	1.689	0.901
61	IGFBP-2	SCFsR	GAPDH, liver	PTN	BTK	IL-15Ra	0.84	0.847	1.687	0.901
62	C1s	Kallikrein7	ERBB1	RAC1	PTN	MEK1	0.826	0.855	1.681	0.893
63	MIP-5	SCFsR	RAC1	C9	PTN	GAPDH, liver	0.845	0.841	1.686	0.901
64	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	Midkine	0.85	0.838	1.688	0.911
65	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin	PARC	0.854	0.849	1.704	0.904
66	C1s	KPCI	ERBB1	CK-MB	BTK	Renin	0.864	0.818	1.682	0.882
67	CD30Ligand	KPCI	PTN	SCFsR	C9	TCTP	0.864	0.827	1.691	0.891
68	PARC	LRIG3	SCFsR	HSP90a	PTN	UBE2N	0.854	0.844	1.698	0.906
69	IGFBP-2	CyclophilinA	ERBB1	Kallikrein7	Ubiquitin + 1	SCFsR	0.864	0.83	1.693	0.899
70	PTN	GAPDH, liver	IGFBP-2	LRIG3	HSP90a	sL-Selectin	0.854	0.852	1.707	0.902
71	CDK5-p35	SCFsR	AMPM2	IGFBP-2	BLC	PARC	0.845	0.83	1.675	0.891
72	PTN	RAC1	ERBB1	BMP-1	Kallikrein7	C1s	0.826	0.864	1.69	0.901
73	CNDP1	ERBB1	HSP90a	CDK5-p35	PTN	Kallikrein7	0.84	0.855	1.695	0.903
74	C1s	PTN	ERBB1	UBE2N	LDH-H1	Contactin-5	0.836	0.852	1.688	0.891
75	Endostatin	Kallikrein7	HSP90a	CK-MB	ERBB1	BTK	0.859	0.832	1.692	0.898

TABLE 18-continued

76	PARC	LRIG3	HSP90a	CK-MB	FGF-17	Kallikrein7	0.836	0.858	1.694	0.896
77	Kallikrein7	RAC1	SCFsR	ERBB1	IGFBP-2	FYN	0.85	0.838	1.688	0.898
78	IL-15Ra	UBE2N	PTN	LRIG3	Kallikrein7	CK-MB	0.831	0.855	1.686	0.898
79	Kallikrein7	GAPDH, liver	ERBB1	CD30Ligand	PTN	MEK1	0.831	0.849	1.68	0.894
80	PTN	GAPDH, liver	IGFBP-2	Kallikrein7	MIP-5	UBE2N	0.845	0.838	1.683	0.891
81	BTK	KPCI	SCFsR	ERBB1	Midkine	CDK5-p35	0.859	0.827	1.686	0.888
82	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand	Prothrombin	0.864	0.838	1.702	0.908
83	CD30Ligand	Kallikrein7	KPCI	SCFsR	Renin	HSP90a	0.854	0.827	1.681	0.881
84	CK-MB	ERBB1	HSP90a	SCFsR	KPCI	TCTP	0.869	0.821	1.69	0.88
85	Ubiquitin + 1	BTK	ERBB1	IGFBP-2	Kallikrein7	SCFsR	0.859	0.832	1.692	0.899
86	CD30Ligand	RAC1	PTN	sL-Selectin	Kallikrein7	IGFBP-2	0.859	0.847	1.706	0.905
87	PARC	AMPM2	ERBB1	CSK	CK-MB	BLC	0.84	0.832	1.673	0.891
88	C1s	PTN	ERBB1	CyclophilinA	Kallikrein7	BMP-1	0.826	0.864	1.69	0.901
89	PTN	SCFsR	GAPDH, liver	HSP90a	LRIG3	CNDP1	0.84	0.855	1.695	0.905
90	C1s	Kallikrein7	ERBB1	RAC1	PTN	Contactin-5	0.831	0.855	1.686	0.896
91	SCFsR	C9	CSK	Kallikrein7	Endostatin	Prothrombin	0.859	0.832	1.692	0.896
92	Kallikrein7	SCFsR	HSP90a	C9	Prothrombin	FGF-17	0.864	0.83	1.693	0.893
93	IGFBP-2	SCFsR	RAC1	ERBB1	CDK5-p35	FYN	0.84	0.847	1.687	0.9
94	IL-15Ra	PTN	RAC1	sL-Selectin	C1s	LRIG3	0.859	0.827	1.686	0.902
95	SCFsR	ERBB1	LDH-H1	CyclophilinA	Kallikrein7	MEK1	0.845	0.835	1.68	0.884
96	IGFBP-2	SCFsR	GAPDH, liver	PTN	MIP-5	RAC1	0.845	0.838	1.683	0.904
97	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	C9	Midkine	0.836	0.849	1.685	0.888
98	PARC	IGFBP-2	HSP90a	PTN	Prothrombin	Renin	0.831	0.849	1.68	0.896
99	IGFBP-2	TCTP	SCFsR	ERBB1	PARC	CDK5-p35	0.822	0.866	1.688	0.898
100	PTN	SCFsR	BTK	IGFBP-2	C1s	Ubiquitin + 1	0.85	0.841	1.691	0.909

Marker	Count	Marker	Count
PTN	56	LDH-H1	8
Kallikrein7	52	CSK	8
SCFsR	49	UBE2N	7
ERBB1	49	AMPM2	7
IGFBP-2	39	sL-Selectin	6
HSP90a	30	Ubiquitin + 1	6
CK-MB	26	TCTP	6
RAC1	21	Renin	6
LRIG3	21	Midkine	6
CD30Ligand	21	MIP-5	6
PARC	18	MEK1	6
BTK	15	IL-15Ra	6
KPCI	14	FYN	6
CDK5-p35	14	FGF-17	6
GAPDH, liver	13	Endostatin	6
C1s	13	Contactin-5	6
CyclophilinA	11	CNDP1	6
C9	10	BMP-1	6
Prothrombin	8	BLC	6

TABLE 19

100 Panels of 7 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers				Sensitivity	Specificity	Sens. + Spec.	AUC
1	LRIG3	IGFBP-2	AMPM2	SCFsR	0.878	0.844	1.722	0.897
		Kallikrein7	PARC	CD30Ligand				
2	CSK	KPCI	ERBB1	CK-MB	0.864	0.838	1.702	0.893
		BLC	SCFsR	PARC				
3	GAPDH, liver	HSP90a	BMP-1	PTN	0.85	0.869	1.719	0.905
		PARC	LRIG3	Kallikrein7				
4	BTK	IGFBP-2	PTN	Kallikrein7	0.887	0.844	1.731	0.898
		SCFsR	KPCI	CD30Ligand				
5	C1s	PTN	ERBB1	UBE2N	0.845	0.881	1.726	0.91
		Kallikrein7	LDH-H1	CK-MB				
6	CD30Ligand	SCFsR	RAC1	C9	0.873	0.855	1.728	0.907
		PTN	LRIG3	HSP90a				
7	CK-MB	Kallikrein7	HSP90a	PARC	0.859	0.869	1.728	0.907
		CDK5-p35	LRIG3	Endostatin				
8	PTN	GAPDH, liver	IGFBP-2	LRIG3	0.854	0.866	1.721	0.911
		SCFsR	HSP90a	CNDP1				
9	LDH-H1	Kallikrein7	ERBB1	HSP90a	0.836	0.881	1.716	0.904
		PTN	CK-MB	Contactin-5				
10	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	0.859	0.866	1.726	0.916
		CD30Ligand	PTN	PARC				
11	Endostatin	Kallikrein7	HSP90a	CK-MB	0.85	0.872	1.722	0.902
		FGF-17	LRIG3	PARC				

TABLE 19-continued

12	IGFBP-2	KPCI	CD30Ligand	SCFsR	0.883	0.832	1.715	0.894
		PTN	FYN	Kallikrein7				
13	PTN	GAPDH, liver	IGFBP-2	LRIG3	0.85	0.858	1.708	0.905
		SCFsR	IL-15Ra	Kallikrein7				
14	Kallikrein7	RAC1	SCFsR	ERBB1	0.854	0.858	1.712	0.901
		IGFBP-2	MEK1	CDK5-p35				
15	Kallikrein7	SCFsR	HSP90a	PTN	0.878	0.841	1.719	0.894
		KPCI	IGFBP-2	MIP-5				
16	Kallikrein7	SCFsR	HSP90a	PTN	0.873	0.844	1.717	0.892
		KPCI	IGFBP-2	Midkine				
17	Prothrombin	IGFBP-2	HSP90a	PTN	0.869	0.861	1.729	0.912
		GAPDH, liver	PARC	SCFsR				
18	LRIG3	ERBB1	HSP90a	SCFsR	0.878	0.835	1.713	0.893
		Kallikrein7	CSK	Renin				
19	CD30Ligand	sL-Selectin	GAPDH, liver	PTN	0.869	0.847	1.715	0.894
		IGFBP-2	Kallikrein7	TCTP				
20	PTN	GAPDH, liver	IGFBP-2	LRIG3	0.864	0.852	1.716	0.913
		SCFsR	CD30Ligand	Ubiquitin + 1				
21	SCFsR	ERBB1	BTK	IGFBP-2	0.878	0.844	1.722	0.899
		CDK5-p35	Kallikrein7	AMPM2				
22	CSK	KPCI	ERBB1	CK-MB	0.878	0.824	1.702	0.896
		BLC	SCFsR	C9				
23	Prothrombin	IGFBP-2	HSP90a	PTN	0.85	0.864	1.713	0.907
		GAPDH, liver	SCFsR	BMP-1				
24	CD30Ligand	RAC1	PTN	sL-Selectin	0.854	0.866	1.721	0.913
		Kallikrein7	ERBB1	C1s				
25	LRIG3	KPCI	IGFBP-2	SCFsR	0.864	0.855	1.719	0.9
		CNDP1	HSP90a	PTN				
26	IGFBP-2	KPCI	CD30Ligand	PTN	0.883	0.83	1.712	0.898
		Contactin-5	SCFsR	BTK				
27	CD30Ligand	CyclophilinA	PTN	sL-Selectin	0.873	0.852	1.726	0.898
		IGFBP-2	Kallikrein7	GAPDH, liver				
28	SCFsR	ERBB1	LDH-H1	CyclophilinA	0.873	0.847	1.72	0.904
		Kallikrein7	FGF-17	C9				
29	IGFBP-2	SCFsR	RAC1	ERBB1	0.845	0.869	1.714	0.909
		PTN	FGF-17	FYN				
30	IL-15Ra	PTN	RAC1	sL-Selectin	0.854	0.852	1.707	0.905
		Kallikrein7	CD30Ligand	LRIG3				
31	CD30Ligand	Kallikrein7	KPCI	PTN	0.873	0.838	1.711	0.889
		IGFBP-2	SCFsR	MEK1				
32	CD30Ligand	Kallikrein7	KPCI	PTN	0.892	0.827	1.719	0.897
		IGFBP-2	SCFsR	MIP-5				
33	CD30Ligand	IGFBP-2	PTN	sL-Selectin	0.864	0.852	1.716	0.906
		RAC1	Midkine	Kallikrein7				
34	CD30Ligand	CyclophilinA	PTN	sL-Selectin	0.859	0.852	1.711	0.902
		Kallikrein7	Renin	IGFBP-2				
35	IGFBP-2	SCFsR	KPCI	PTN	0.873	0.841	1.714	0.893
		TCTP	CD30Ligand	Kallikrein7				
36	PTN	SCFsR	UBE2N	IGFBP-2	0.887	0.849	1.737	0.896
		CD30Ligand	Kallikrein7	KPCI				
37	Ubiquitin + 1	BTK	ERBB1	IGFBP-2	0.864	0.852	1.716	0.899
		Kallikrein7	SCFsR	Midkine				
38	PTN	SCFsR	AMPM2	IGFBP-2	0.873	0.847	1.72	0.889
		Kallikrein7	CD30Ligand	KPCI				
39	CD30Ligand	SCFsR	ERBB1	CSK	0.869	0.83	1.698	0.898
		KPCI	PTN	BLC				
40	PTN	RAC1	IGFBP-2	PARC	0.836	0.875	1.711	0.913
		SCFsR	HSP90a	BMP-1				
41	PTN	KPCI	IGFBP-2	Prothrombin	0.859	0.858	1.717	0.894
		HSP90a	SCFsR	C1s				
42	CK-MB	Kallikrein7	HSP90a	LRIG3	0.854	0.861	1.715	0.902
		PTN	LDH-H1	CNDP1				
43	CD30Ligand	IGFBP-2	PTN	sL-Selectin	0.836	0.875	1.711	0.91
		RAC1	Contactin-5	PARC				
44	CD30Ligand	sL-Selectin	GAPDH, liver	PTN	0.873	0.844	1.717	0.9
		BTK	Kallikrein7	Endostatin				
45	Kallikrein7	RAC1	SCFsR	ERBB1	0.859	0.855	1.714	0.904
		IGFBP-2	FYN	CD30Ligand				
46	CD30Ligand	IGFBP-2	PTN	sL-Selectin	0.831	0.875	1.706	0.901
		RAC1	IL-15Ra	PARC				
47	BTK	KPCI	ERBB1	CD30Ligand	0.859	0.847	1.706	0.891
		PTN	SCFsR	MEK1				
48	SCFsR	C9	CSK	Kallikrein7	0.878	0.827	1.705	0.896
		Endostatin	Prothrombin	MIP-5				
49	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	0.85	0.858	1.708	0.908
		CD30Ligand	PTN	Renin				
50	IGFBP-2	TCTP	SCFsR	ERBB1	0.873	0.838	1.711	0.894
		Kallikrein7	CDK5-p35	AMPM2				
51	UBE2N	HSP90a	ERBB1	PTN	0.864	0.855	1.719	0.914
		Kallikrein7	CK-MB	CDK5-p35				

TABLE 19-continued

52	CD30Ligand	Kallikrein7	KPCI	PTN	0.887	0.827	1.714	0.897
		IGFBP-2	SCFsR	Ubiquitin + 1				
53	CSK	KPCI	ERBB1	CK-MB	0.873	0.821	1.694	0.893
		BLC	SCFsR	LRIG3				
54	C1s	PTN	ERBB1	CyclophilinA	0.836	0.875	1.711	0.907
		Kallikrein7	BMP-1	sL-Selectin				
55	CK-MB	SCFsR	CSK	ERBB1	0.883	0.832	1.715	0.891
		KPCI	CNDP1	FGF-17				
56	CK-MB	SCFsR	CSK	ERBB1	0.878	0.832	1.71	0.889
		C9	KPCI	Contactin-5				
57	Prothrombin	IGFBP-2	HSP90a	PTN	0.864	0.849	1.713	0.901
		GAPDH, liver	SCFsR	FYN				
58	SCFsR	ERBB1	CSK	PARC	0.822	0.884	1.705	0.9
		CDK5-p35	IGFBP-2	IL-15Ra				
59	Kallikrein7	SCFsR	HSP90a	PTN	0.836	0.869	1.705	0.897
		LRIG3	IGFBP-2	MEK1				
60	LRIG3	KPCI	CNDP1	SCFsR	0.869	0.835	1.704	0.897
		MIP-5	PTN	IGFBP-2				
61	CD30Ligand	IGFBP-2	PTN	RAC1	0.859	0.852	1.711	0.905
		SCFsR	Midkine	LDH-H1				
62	PTN	SCFsR	AMPM2	IGFBP-2	0.873	0.832	1.706	0.901
		Kallikrein7	CD30Ligand	Renin				
63	CD30Ligand	PTN	ERBB1	TCTP	0.85	0.858	1.708	0.9
		IGFBP-2	Kallikrein7	Contactin-5				
64	PTN	GAPDH, liver	IGFBP-2	LRIG3	0.859	0.858	1.717	0.915
		SCFsR	CD30Ligand	UBE2N				
65	C1s	PTN	ERBB1	CyclophilinA	0.84	0.872	1.713	0.909
		SCFsR	PARC	Ubiquitin + 1				
66	CDK5-p35	CSK	ERBB1	PARC	0.831	0.861	1.692	0.897
		CK-MB	SCFsR	BLC				
67	KPCI	HSP90a	PTN	Kallikrein7	0.854	0.855	1.71	0.896
		IGFBP-2	BMP-1	SCFsR				
68	CD30Ligand	SCFsR	KPCI	C9	0.859	0.855	1.714	0.901
		BTK	PTN	Endostatin				
69	PARC	LRIG3	SCFsR	HSP90a	0.845	0.872	1.717	0.905
		Kallikrein7	CK-MB	FGF-17				
70	Prothrombin	IGFBP-2	HSP90a	SCFsR	0.859	0.852	1.711	0.901
		ERBB1	Kallikrein7	FYN				
71	sL-Selectin	LRIG3	HSP90a	PTN	0.85	0.855	1.705	0.908
		Prothrombin	IL-15Ra	PARC				
72	Kallikrein7	GAPDH, liver	ERBB1	CD30Ligand	0.85	0.855	1.705	0.896
		PTN	MEK1	BTK				
73	IGFBP-2	SCFsR	GAPDH, liver	PTN	0.845	0.858	1.703	0.912
		MIP-5	RAC1	PARC				
74	Kallikrein7	SCFsR	HSP90a	PTN	0.836	0.875	1.711	0.906
		LRIG3	IGFBP-2	Midkine				
75	Prothrombin	CK-MB	HSP90a	LRIG3	0.859	0.844	1.703	0.899
		Endostatin	Kallikrein7	Renin				
76	CK-MB	ERBB1	HSP90a	SCFsR	0.869	0.838	1.707	0.887
		KPCI	TCTP	PARC				
77	PTN	SCFsR	UBE2N	IGFBP-2	0.864	0.852	1.716	0.904
		CD30Ligand	LDH-H1	CDK5-p35				
78	LRIG3	SCFsR	HSP90a	PTN	0.854	0.858	1.712	0.905
		Ubiquitin + 1	CD30Ligand	IGFBP-2				
79	SCFsR	ERBB1	AMPM2	IGFBP-2	0.854	0.861	1.715	0.902
		CDK5-p35	PARC	BTK				
80	CSK	KPCI	ERBB1	CK-MB	0.859	0.832	1.692	0.89
		BLC	SCFsR	FGF-17				
81	CD30Ligand	IGFBP-2	PTN	CyclophilinA	0.869	0.841	1.709	0.898
		SCFsR	KPCI	BMP-1				
82	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	0.84	0.875	1.715	0.918
		C1s	PARC	PTN				
83	CNDP1	SCFsR	HSP90a	PTN	0.859	0.855	1.714	0.906
		ERBB1	GAPDH, liver	BTK				
84	CK-MB	SCFsR	CSK	ERBB1	0.864	0.844	1.708	0.886
		KPCI	PARC	Contactin-5				
85	IGFBP-2	SCFsR	RAC1	ERBB1	0.859	0.852	1.711	0.905
		CDK5-p35	FYN	Kallikrein7				
86	BTK	KPCI	ERBB1	CD30Ligand	0.864	0.841	1.705	0.899
		PTN	SCFsR	IL-15Ra				
87	IGFBP-2	SCFsR	KPCI	PTN	0.864	0.841	1.705	0.887
		C1s	Kallikrein7	MEK1				
88	KPCI	HSP90a	IGFBP-2	SCFsR	0.859	0.844	1.703	0.895
		PTN	LRIG3	MIP-5				
89	LRIG3	CNDP1	HSP90a	CK-MB	0.831	0.878	1.709	0.903
		PTN	Kallikrein7	Midkine				
90	PTN	KPCI	IGFBP-2	Prothrombin	0.878	0.824	1.702	0.891
		HSP90a	SCFsR	Renin				
91	CK-MB	SCFsR	TCTP	ERBB1	0.845	0.861	1.706	0.902
		CD30Ligand	PARC	GAPDH, liver				

TABLE 19-continued

92	PTN	LRIG3	HSP90a	UBE2N	0.854	0.861	1.715	0.906
		SCFsR	IGFBP-2	CD30Ligand				
93	Kallikrein7	C9	ERBB1	CyclophilinA	0.869	0.844	1.712	0.905
		SCFsR	Ubiquitin + 1	IGFBP-2				
94	PTN	LRIG3	AMPM2	IGFBP-2	0.869	0.847	1.715	0.888
		Prothrombin	sL-Selectin	Kallikrein7				
95	CK-MB	SCFsR	CSK	ERBB1	0.859	0.832	1.692	0.89
		KPCI	FGF-17	BLC				
96	CNDP1	SCFsR	BTK	PTN	0.85	0.858	1.708	0.908
		GAPDH, liver	BMP-1	sL-Selectin				
97	CD30Ligand	SCFsR	ERBB1	KPCI	0.864	0.841	1.705	0.891
		CK-MB	BTK	Contactin-5				
98	Endostatin	SCFsR	HSP90a	LRIG3	0.864	0.849	1.713	0.911
		PTN	Prothrombin	CDK5-p35				
99	LRIG3	CNDP1	HSP90a	CK-MB	0.836	0.875	1.711	0.902
		PTN	Kallikrein7	FYN				
100	BTK	GAPDH, liver	ERBB1	PARC	0.84	0.864	1.704	0.901
		CK-MB	IL-15Ra	LRIG3				

Marker	Count	Marker	Count
SCFsR	75	CNDP1	9
PTN	69	IL-15Ra	7
IGFBP-2	58	FYN	7
Kallikrein7	53	FGF-17	7
CD30Ligand	39	Endostatin	7
ERBB1	38	Contactin-5	7
KPCI	33	C9	7
HSP90a	33	C1s	7
LRIG3	28	BMP-1	7
CK-MB	23	BLC	7
PARC	22	AMPM2	7
GAPDH, liver	17	Ubiquitin + 1	6
BTK	14	UBE2N	6
sL-Selectin	13	TCTP	6
RAC1	13	Renin	6
CSK	13	Midkine	6
Prothrombin	11	MIP-5	6
CDK5-p35	11	MEK1	6
CyclophilinA	10	LDH-H1	6

TABLE 20

100 Panels of 8 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers				Sensitivity	Specificity	Sens. + Spec.	AUC
1	LRIG3	IGFBP-2	AMPM2	SCFsR	0.869	0.866	1.735	0.907
	Kallikrein7	PARC	CD30Ligand	CK-MB				
2	CD30Ligand	CyclophilinA	PTN	ERBB1	0.85	0.869	1.719	0.914
	GAPDH, liver	SCFsR	Kallikrein7	BLC				
3	PTN	CyclophilinA	BMP-1	ERBB1	0.854	0.875	1.729	0.917
	Kallikrein7	GAPDH, liver	SCFsR	CD30Ligand				
4	CD30Ligand	Kallikrein7	KPCI	PTN	0.897	0.855	1.752	0.904
	IGFBP-2	SCFsR	C9	BTK				
5	IGFBP-2	SCFsR	KPCI	PTN	0.892	0.849	1.741	0.901
	C1s	CD30Ligand	Ubiquitin + 1	Kallikrein7				
6	CDK5-p35	IGFBP-2	HSP90a	PTN	0.873	0.861	1.734	0.902
	SCFsR	KPCI	Kallikrein7	CD30Ligand				
7	Endostatin	LRIG3	HSP90a	PTN	0.869	0.872	1.741	0.912
	CNDP1	Kallikrein7	CK-MB	BTK				
8	CK-MB	SCFsR	CSK	ERBB1	0.887	0.847	1.734	0.893
	KPCI	CDK5-p35	HSP90a	PARC				
9	IGFBP-2	KPCI	CD30Ligand	PTN	0.901	0.83	1.731	0.901
	Contactin-5	SCFsR	Kallikrein7	BTK				
10	IGFBP-2	SCFsR	GAPDH, liver	HSP90a	0.869	0.869	1.738	0.917
	PTN	FGF-17	PARC	Prothrombin				
11	PTN	RAC1	IGFBP-2	PARC	0.873	0.864	1.737	0.92
	SCFsR	Kallikrein7	CD30Ligand	FYN				
12	BTK	IGFBP-2	PTN	Kallikrein7	0.897	0.835	1.732	0.898
	SCFsR	KPCI	IL-15Ra	CD30Ligand				
13	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	0.883	0.858	1.741	0.91
	CD30Ligand	PTN	Renin	LDH-H1				
14	CD30Ligand	CyclophilinA	PTN	ERBB1	0.864	0.861	1.725	0.907
	GAPDH, liver	SCFsR	Kallikrein7	MEK1				
15	IGFBP-2	SCFsR	GAPDH, liver	PTN	0.859	0.875	1.734	0.914
	MIP-5	RAC1	PARC	C1s				

TABLE 20-continued

16	CD30Ligand	Kallikrein7	KPCI	PTN	0.906	0.821	1.727	0.897
	IGFBP-2	SCFsR	MIP-5	Midkine				
17	CD30Ligand	KPCI	PTN	SCFsR	0.887	0.849	1.737	0.9
	C9	TCTP	Kallikrein7	IGFBP-2				
18	SCFsR	C9	UBE2N	CD30Ligand	0.892	0.852	1.744	0.902
	PTN	KPCI	Kallikrein7	IGFBP-2				
19	PARC	GAPDH, liver	HSP90a	PTN	0.869	0.866	1.735	0.912
	IGFBP-2	LRIG3	sL-Selectin	Prothrombin				
20	Kallikrein7	ERBB1	AMPM2	IGFBP-2	0.873	0.861	1.734	0.903
	BTK	SCFsR	C9	CDK5-p35				
21	CSK	KPCI	ERBB1	CK-MB	0.873	0.844	1.717	0.894
	BLC	SCFsR	PARC	Renin				
22	CD30Ligand	Kallikrein7	KPCI	PTN	0.887	0.841	1.728	0.9
	IGFBP-2	SCFsR	BMP-1	UBE2N				
23	CNDP1	SCFsR	HSP90a	PTN	0.878	0.855	1.733	0.911
	ERBB1	GAPDH, liver	BTK	CDK5-p35				
24	KPCI	HSP90a	IGFBP-2	SCFsR	0.878	0.852	1.73	0.899
	PTN	LRIG3	Kallikrein7	Contactin-5				
25	PARC	LRIG3	SCFsR	HSP90a	0.854	0.881	1.735	0.908
	Kallikrein7	CK-MB	Endostatin	FGF-17				
26	IGFBP-2	KPCI	CD30Ligand	SCFsR	0.883	0.849	1.732	0.903
	PTN	FYN	Kallikrein7	ERBB1				
27	PTN	SCFsR	BTK	IGFBP-2	0.878	0.847	1.725	0.897
	C1s	Kallikrein7	KPCI	IL-15Ra				
28	CD30Ligand	IGFBP-2	PTN	RAC1	0.864	0.875	1.739	0.915
	SCFsR	C9	LRIG3	LDH-H1				
29	PTN	SCFsR	RAC1	C1s	0.845	0.875	1.72	0.902
	IGFBP-2	LDH-H1	MEK1	PARC				
30	PTN	SCFsR	AMPM2	IGFBP-2	0.869	0.858	1.726	0.902
	Kallikrein7	CD30Ligand	LRIG3	Midkine				
31	IGFBP-2	TCTP	SCFsR	ERBB1	0.85	0.881	1.73	0.912
	PARC	CDK5-p35	Kallikrein7	CK-MB				
32	CD30Ligand	Kallikrein7	KPCI	PTN	0.892	0.841	1.733	0.901
	IGFBP-2	SCFsR	Ubiquitin + 1	LRIG3				
33	CD30Ligand	RAC1	PTN	sL-Selectin	0.864	0.869	1.733	0.92
	Kallikrein7	IGFBP-2	C1s	PARC				
34	CSK	KPCI	ERBB1	CK-MB	0.873	0.841	1.714	0.892
	BLC	SCFsR	PARC	AMPM2				
35	CD30Ligand	Kallikrein7	KPCI	PTN	0.878	0.849	1.727	0.899
	IGFBP-2	SCFsR	BMP-1	HSP90a				
36	PTN	KPCI	IGFBP-2	Prothrombin	0.878	0.852	1.73	0.899
	HSP90a	SCFsR	CNDP1	LRIG3				
37	PARC	LRIG3	SCFsR	HSP90a	0.84	0.889	1.73	0.903
	Kallikrein7	CK-MB	Endostatin	Contactin-5				
38	CD30Ligand	IGFBP-2	PTN	RAC1	0.859	0.878	1.737	0.915
	SCFsR	FGF-17	LDH-H1	PARC				
39	KPCI	HSP90a	PTN	Kallikrein7	0.873	0.858	1.731	0.898
	IGFBP-2	CD30Ligand	ERBB1	FYN				
40	CD30Ligand	IGFBP-2	PTN	RAC1	0.883	0.841	1.724	0.897
	SCFsR	Kallikrein7	KPCI	IL-15Ra				
41	IGFBP-2	CyclophilinA	ERBB1	Kallikrein7	0.873	0.847	1.72	0.899
	Ubiquitin + 1	SCFsR	MEK1	C9				
42	LRIG3	KPCI	CNDP1	SCFsR	0.883	0.847	1.729	0.901
	MIP-5	PTN	IGFBP-2	CDK5-p35				
43	SCFsR	ERBB1	BTK	IGFBP-2	0.883	0.844	1.726	0.907
	CDK5-p35	Kallikrein7	Ubiquitin + 1	Midkine				
44	BTK	IGFBP-2	PTN	Kallikrein7	0.897	0.841	1.738	0.903
	SCFsR	KPCI	CD30Ligand	Renin				
45	LRIG3	ERBB1	HSP90a	SCFsR	0.873	0.852	1.726	0.905
	Kallikrein7	TCTP	PTN	LDH-H1				
46	C1s	IGFBP-2	PTN	UBE2N	0.887	0.849	1.737	0.9
	Kallikrein7	SCFsR	KPCI	CD30Ligand				
47	PTN	RAC1	IGFBP-2	PARC	0.854	0.878	1.732	0.913
	sL-Selectin	CD30Ligand	Kallikrein7	FGF-17				
48	CDK5-p35	CSK	ERBB1	PARC	0.859	0.852	1.711	0.908
	CK-MB	SCFsR	GAPDH, liver	BLC				
49	SCFsR	BMP-1	HSP90a	PTN	0.864	0.861	1.725	0.899
	PARC	BTK	KPCI	ERBB1				
50	IGFBP-2	KPCI	CD30Ligand	PTN	0.883	0.847	1.729	0.898
	Contactin-5	SCFsR	Kallikrein7	UBE2N				
51	PTN	SCFsR	AMPM2	IGFBP-2	0.873	0.858	1.731	0.903
	Kallikrein7	CD30Ligand	LRIG3	Endostatin				
52	CD30Ligand	Kallikrein7	KPCI	PTN	0.887	0.844	1.731	0.901
	IGFBP-2	SCFsR	C9	FYN				
53	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	0.878	0.844	1.722	0.896
	CD30Ligand	PTN	KPCI	IL-15Ra				
54	Kallikrein7	RAC1	SCFsR	ERBB1	0.859	0.858	1.717	0.902
	IGFBP-2	CDK5-p35	Midkine	MEK1				
55	CD30Ligand	Kallikrein7	KPCI	PTN	0.897	0.832	1.729	0.901
	IGFBP-2	SCFsR	MIP-5	RAC1				

TABLE 20-continued

56	CD30Ligand	SCFsR	KPCI	C9	0.887	0.855	1.742	0.899
	ERBB1	HSP90a	Prothrombin	Kallikrein7				
57	Kallikrein7	SCFsR	HSP90a	PTN	0.892	0.841	1.733	0.902
	KPCI	CD30Ligand	IGFBP-2	Renin				
58	PTN	RAC1	IGFBP-2	PARC	0.887	0.838	1.725	0.912
	SCFsR	Kallikrein7	CD30Ligand	TCTP				
59	PTN	RAC1	IGFBP-2	PARC	0.864	0.866	1.73	0.922
	SCFsR	Kallikrein7	sL-Selectin	CD30Ligand				
60	CSK	KPCI	ERBB1	CK-MB	0.873	0.838	1.711	0.898
	BLC	SCFsR	PARC	LRIG3				
61	Kallikrein7	BMP-1	HSP90a	PTN	0.878	0.847	1.725	0.91
	LRIG3	PARC	RAC1	IGFBP-2				
62	LRIG3	CNDP1	HSP90a	CK-MB	0.859	0.869	1.728	0.913
	PTN	GAPDH, liver	Kallikrein7	PARC				
63	Prothrombin	CK-MB	HSP90a	LRIG3	0.864	0.864	1.727	0.902
	Endostatin	Kallikrein7	SCFsR	Contactin-5				
64	CD30Ligand	IGFBP-2	PTN	RAC1	0.864	0.872	1.736	0.921
	SCFsR	FGF-17	GAPDH, liver	PARC				
65	PARC	Kallikrein7	HSP90a	ERBB1	0.864	0.866	1.73	0.911
	IGFBP-2	FYN	SCFsR	CDK5-p35				
66	Kallikrein7	SCFsR	HSP90a	PTN	0.869	0.852	1.721	0.896
	KPCI	CD30Ligand	IGFBP-2	IL-15Ra				
67	Kallikrein7	RAC1	SCFsR	ERBB1	0.859	0.858	1.717	0.901
	C9	BTK	IGFBP-2	MEK1				
68	CD30Ligand	Kallikrein7	KPCI	PTN	0.901	0.827	1.728	0.898
	IGFBP-2	SCFsR	MIP-5	UBE2N				
69	IGFBP-2	KPCI	CD30Ligand	SCFsR	0.883	0.844	1.726	0.896
	PTN	GAPDH, liver	Kallikrein7	Midkine				
70	IGFBP-2	SCFsR	KPCI	PTN	0.878	0.852	1.73	0.9
	C1s	Kallikrein7	HSP90a	Renin				
71	FGF-17	Kallikrein7	ERBB1	GAPDH, liver	0.878	0.847	1.725	0.912
	C9	SCFsR	TCTP	PTN				
72	SCFsR	ERBB1	BTK	IGFBP-2	0.854	0.878	1.732	0.914
	CDK5-p35	Kallikrein7	Ubiquitin + 1	PARC				
73	CD30Ligand	sL-Selectin	GAPDH, liver	PTN	0.878	0.852	1.73	0.906
	IGFBP-2	RAC1	Kallikrein7	LRIG3				
74	PTN	SCFsR	AMPM2	IGFBP-2	0.887	0.847	1.734	0.892
	Kallikrein7	CD30Ligand	KPCI	BTK				
75	CSK	KPCI	ERBB1	CK-MB	0.873	0.838	1.711	0.894
	BLC	SCFsR	PARC	GAPDH, liver				
76	CD30Ligand	Kallikrein7	KPCI	PTN	0.883	0.841	1.724	0.901
	IGFBP-2	SCFsR	BMP-1	CyclophilinA				
77	Endostatin	LRIG3	HSP90a	PTN	0.85	0.878	1.728	0.905
	CNDP1	Kallikrein7	CK-MB	LDH-H1				
78	IGFBP-2	SCFsR	KPCI	PTN	0.869	0.855	1.724	0.896
	C1s	Kallikrein7	HSP90a	Contactin-5				
79	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	0.864	0.866	1.73	0.913
	CD30Ligand	PTN	PARC	FYN				
80	PTN	GAPDH, liver	IGFBP-2	LRIG3	0.845	0.875	1.72	0.916
	SCFsR	IL-15Ra	HSP90a	PARC				
81	CD30Ligand	Kallikrein7	KPCI	PTN	0.873	0.844	1.717	0.893
	IGFBP-2	SCFsR	MEK1	LRIG3				
82	CD30Ligand	Kallikrein7	KPCI	PTN	0.897	0.83	1.726	0.9
	IGFBP-2	SCFsR	MIP-5	GAPDH, liver				
83	CD30Ligand	Kallikrein7	KPCI	PTN	0.878	0.847	1.725	0.9
	IGFBP-2	LRIG3	SCFsR	Midkine				
84	Prothrombin	IGFBP-2	HSP90a	PTN	0.873	0.866	1.74	0.911
	GAPDH, liver	SCFsR	CD30Ligand	LRIG3				
85	PTN	SCFsR	BTK	IGFBP-2	0.887	0.838	1.725	0.902
	C1s	Kallikrein7	KPCI	Renin				
86	CDK5-p35	KPCI	ERBB1	HSP90a	0.883	0.841	1.724	0.892
	CK-MB	PARC	SCFsR	TCTP				
87	PTN	RAC1	IGFBP-2	PARC	0.887	0.849	1.737	0.92
	SCFsR	Kallikrein7	CD30Ligand	UBE2N				
88	PTN	GAPDH, liver	IGFBP-2	LRIG3	0.864	0.861	1.725	0.921
	SCFsR	PARC	CD30Ligand	Ubiquitin + 1				
89	sL-Selectin	CyclophilinA	ERBB1	Kallikrein7	0.859	0.869	1.728	0.914
	CD30Ligand	PTN	C1s	GAPDH, liver				
90	PTN	SCFsR	AMPM2	IGFBP-2	0.878	0.852	1.73	0.894
	Kallikrein7	CD30Ligand	LRIG3	KPCI				
91	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	0.85	0.861	1.711	0.905
	CD30Ligand	ERBB1	RAC1	BLC				
92	Kallikrein7	BMP-1	HSP90a	PTN	0.864	0.858	1.722	0.91
	LRIG3	PARC	UBE2N	IGFBP-2				
93	LRIG3	CNDP1	HSP90a	PTN	0.864	0.864	1.727	0.911
	Prothrombin	GAPDH, liver	SCFsR	IGFBP-2				
94	CD30Ligand	Kallikrein7	KPCI	PTN	0.887	0.844	1.731	0.902
	IGFBP-2	SCFsR	C9	CSK				
95	IGFBP-2	KPCI	CD30Ligand	PTN	0.887	0.835	1.723	0.9
	Contactin-5	SCFsR	Kallikrein7	LRIG3				

TABLE 20-continued

96	CD30Ligand	Kallikrein7	KPCI	PTN	0.878	0.852	1.73	0.901
	IGFBP-2	LRIG3	SCFsR	Endostatin				
97	Kallikrein7	SCFsR	KPCI	HSP90a	0.878	0.858	1.736	0.904
	FGF-17	IGFBP-2	PTN	PARC				
98	CD30Ligand	IGFBP-2	PTN	RAC1	0.869	0.861	1.729	0.91
	SCFsR	C9	LDH-H1	FYN				
99	BTK	IGFBP-2	PTN	Kallikrein7	0.873	0.847	1.72	0.898
	SCFsR	KPCI	IL-15Ra	C9				
100	CD30Ligand	Kallikrein7	KPCI	PTN	0.873	0.844	1.717	0.891
	IGFBP-2	SCFsR	MEK1	BTK				

Marker	Count	Marker	Count
SCFsR	89	Prothrombin	7
PTN	79	MEK1	7
IGFBP-2	78	LDH-H1	7
Kallikrein7	77	IL-15Ra	7
CD30Ligand	58	FYN	7
KPCI	51	FGF-17	7
PARC	33	Endostatin	7
HSP90a	30	Contactin-5	7
LRIG3	29	CSK	7
ERBB1	27	CNDP1	7
GAPDH, liver	20	BMP-1	7
RAC1	19	BLC	7
BTK	16	AMPM2	7
CK-MB	15	sL-Selectin	6
C9	13	Ubiquitin + 1	6
CDK5-p35	12	TCTP	6
CyclophilinA	10	Renin	6
C1s	10	Midkine	6
UBE2N	7	MIP-5	6

TABLE 21

100 Panels of 9 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers					Sensitivity	Specificity	Sens. + Spec.	AUC
1	Kallikrein7	SCFsR	HSP90a	ERBB1	CDK5-p35	0.887	0.858	1.745	0.905
	IGFBP-2	AMPM2	PARC	FYN					
2	CSK	KPCI	ERBB1	CK-MB	BLC	0.883	0.847	1.729	0.9
	SCFsR	PARC	Renin	CDK5-p35					
3	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	0.883	0.861	1.743	0.917
	PARC	RAC1	IGFBP-2	Renin					
4	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.878	0.881	1.759	0.922
	Kallikrein7	CD30Ligand	BTK	Renin					
5	C1s	SCFsR	GAPDH, liver	C9	PTN	0.897	0.855	1.752	0.914
	Prothrombin	CD30Ligand	Kallikrein7	UBE2N					
6	Kallikrein7	LRIG3	HSP90a	PTN	IGFBP-2	0.873	0.872	1.745	0.912
	CK-MB	LDH-H1	CNDP1	SCFsR					
7	IGFBP-2	KPCI	CD30Ligand	PTN	Contactin-5	0.906	0.844	1.75	0.902
	SCFsR	Kallikrein7	RAC1	MIP-5					
8	Kallikrein7	SCFsR	HSP90a	PTN	ERBB1	0.869	0.889	1.758	0.925
	CyclophilinA	IGFBP-2	CK-MB	PARC					
9	CK-MB	LRIG3	HSP90a	SCFsR	PARC	0.873	0.875	1.748	0.915
	Prothrombin	Endostatin	Kallikrein7	BTK					
10	CDK5-p35	IGFBP-2	HSP90a	PTN	SCFsR	0.878	0.872	1.75	0.906
	KPCI	Kallikrein7	PARC	FGF-17					
11	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	0.883	0.852	1.735	0.9
	KPCI	IL-15Ra	C9	HSP90a					
12	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.883	0.852	1.735	0.893
	SCFsR	MEK1	LRIG3	Midkine					
13	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.883	0.864	1.746	0.903
	SCFsR	C9	LRIG3	TCTP					
14	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.901	0.849	1.751	0.904
	SCFsR	Ubiquitin + 1	BTK	C9					
15	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.883	0.869	1.752	0.922
	Kallikrein7	sL-Selectin	FYN	CD30Ligand					
16	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	0.878	0.858	1.736	0.898
	CD30Ligand	LRIG3	CDK5-p35	KPCI					
17	CD30Ligand	SCFsR	ERBB1	CyclophilinA	PTN	0.864	0.864	1.727	0.916
	IGFBP-2	RAC1	Kallikrein7	BLC					
18	CyclophilinA	HSP90a	ERBB1	SCFsR	PARC	0.873	0.869	1.743	0.913
	IGFBP-2	Kallikrein7	BMP-1	CDK5-p35					
19	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	0.906	0.844	1.75	0.906
	Kallikrein7	KPCI	Renin	C1s					

TABLE 21-continued

20	LRIG3	CNDP1	HSP90a	CK-MB	PTN	0.854	0.889	1.744	0.911
		GAPDH, liver	Kallikrein7	Endostatin	C1s				
21	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.887	0.858	1.745	0.903
		SCFsR	C9	CSK	LRIG3				
22	PTN	SCFsR	BTK	IGFBP-2	C1s	0.897	0.849	1.746	0.902
		Kallikrein7	KPCI	C9	Contactin-5				
23	CK-MB	LRIG3	HSP90a	SCFsR	PARC	0.864	0.884	1.747	0.914
		Prothrombin	Endostatin	Kallikrein7	FGF-17				
24	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	0.883	0.852	1.735	0.898
		KPCI	HSP90a	BMP-1	IL-15Ra				
25	Prothrombin	IGFBP-2	HSP90a	PTN	GAPDH, liver	0.878	0.866	1.744	0.907
		SCFsR	CD30Ligand	LRIG3	LDH-H1				
26	CD30Ligand	CyclophilinA	PTN	ERBB1	GAPDH, liver	0.864	0.869	1.733	0.91
		IGFBP-2	Kallikrein7	SCFsR	MEK1				
27	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.901	0.838	1.739	0.904
		SCFsR	CDK5-p35	MIP-5	RAC1				
28	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.897	0.849	1.746	0.905
		SCFsR	C9	BTK	Midkine				
29	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	0.883	0.861	1.743	0.908
		TCTP	PTN	C9	LDH-H1				
30	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2	0.878	0.872	1.75	0.92
		LRIG3	SCFsR	C9	UBE2N				
31	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.892	0.847	1.739	0.905
		SCFsR	CDK5-p35	C1s	Ubiquitin + 1				
32	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.883	0.864	1.746	0.923
		CD30Ligand	GAPDH, liver	sL-Selectin	Kallikrein7				
33	Kallikrein7	SCFsR	HSP90a	ERBB1	CDK5-p35	0.878	0.858	1.736	0.905
		IGFBP-2	AMPM2	PARC	BTK				
34	CSK	KPCI	ERBB1	CK-MB	BLC	0.869	0.855	1.724	0.894
		SCFsR	PARC	Renin	Contactin-5				
35	Endostatin	LRIG3	HSP90a	PTN	CNDP1	0.854	0.886	1.741	0.906
		Kallikrein7	CK-MB	LDH-H1	Contactin-5				
36	Prothrombin	IGFBP-2	HSP90a	PTN	GAPDH, liver	0.878	0.866	1.744	0.914
		SCFsR	FYN	PARC	FGF-17				
37	CDK5-p35	LRIG3	HSP90a	PTN	IGFBP-2	0.859	0.875	1.734	0.918
		GAPDH, liver	SCFsR	PARC	IL-15Ra				
38	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2	0.864	0.869	1.733	0.911
		PTN	SCFsR	PARC	MEK1				
39	IGFBP-2	KPCI	CD30Ligand	SCFsR	PTN	0.911	0.827	1.738	0.897
		FYN	Kallikrein7	MIP-5	Midkine				
40	CD30Ligand	KPCI	PTN	SCFsR	C9	0.897	0.838	1.735	0.898
		TCTP	Kallikrein7	IGFBP-2	Prothrombin				
41	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	0.901	0.844	1.745	0.902
		KPCI	CD30Ligand	UBE2N	C9				
42	IGFBP-2	SCFsR	KPCI	PTN	C1s	0.901	0.835	1.737	0.9
		CD30Ligand	Kallikrein7	Midkine	Ubiquitin + 1				
43	PTN	LRIG3	CD30Ligand	GAPDH, liver	PARC	0.878	0.866	1.744	0.918
		HSP90a	SCFsR	Prothrombin	sL-Selectin				
44	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	0.878	0.858	1.736	0.903
		CD30Ligand	LRIG3	Endostatin	FYN				
45	CSK	KPCI	ERBB1	CK-MB	BLC	0.869	0.852	1.721	0.9
		SCFsR	PARC	Renin	PTN				
46	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	0.878	0.864	1.742	0.904
		KPCI	HSP90a	PARC	BMP-1				
47	LRIG3	CNDP1	HSP90a	CK-MB	PTN	0.869	0.872	1.741	0.912
		Kallikrein7	CyclophilinA	Endostatin	C1s				
48	FGF-17	SCFsR	ERBB1	BTK	IGFBP-2	0.869	0.875	1.744	0.923
		Kallikrein7	PARC	RAC1	PTN				
49	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR	0.859	0.875	1.734	0.919
		IL-15Ra	HSP90a	PARC	sL-Selectin				
50	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3	0.854	0.878	1.732	0.908
		IGFBP-2	Prothrombin	PARC	MEK1				
51	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.901	0.835	1.737	0.901
		SCFsR	CDK5-p35	MIP-5	UBE2N				
52	IGFBP-2	TCTP	SCFsR	ERBB1	PARC	0.864	0.866	1.73	0.913
		CDK5-p35	Kallikrein7	CK-MB	UBE2N				
53	IGFBP-2	CyclophilinA	ERBB1	Kallikrein7	Ubiquitin + 1	0.854	0.881	1.735	0.918
		SCFsR	PARC	CK-MB	CD30Ligand				
54	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	0.873	0.861	1.734	0.911
		CD30Ligand	CDK5-p35	ERBB1	BTK				
55	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	0.864	0.855	1.719	0.907
		CD30Ligand	UBE2N	LRIG3	BLC				
56	PTN	CyclophilinA	BMP-1	ERBB1	Kallikrein7	0.873	0.864	1.737	0.914
		GAPDH, liver	SCFsR	CD30Ligand	FYN				
57	Endostatin	LRIG3	HSP90a	CK-MB	PARC	0.864	0.875	1.739	0.914
		GAPDH, liver	Kallikrein7	CNDP1	PTN				
58	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	0.892	0.849	1.741	0.906
		CSK	PTN	LDH-H1	CDK5-p35				
59	CK-MB	LRIG3	HSP90a	SCFsR	PARC	0.864	0.881	1.745	0.91
		Prothrombin	Endostatin	Kallikrein7	Contactin-5				

TABLE 21-continued

60	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	0.864	0.878	1.742	0.922
		FGF-17	GAPDH, liver	LRIG3	PARC				
61	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	0.887	0.847	1.734	0.896
		KPCI	IL-15Ra	C9	FYN				
62	CD30Ligand	CyclophilinA	PTN	ERBB1	GAPDH, liver	0.873	0.858	1.731	0.908
		SCFsR	Kallikrein7	MEK1	CDK5-p35				
63	IGFBP-2	SCFsR	RAC1	C1s	Kallikrein7	0.864	0.872	1.736	0.921
		PARC	GAPDH, liver	PTN	MIP-5				
64	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR	0.873	0.866	1.74	0.911
		HSP90a	Midkine	Prothrombin	CD30Ligand				
65	IGFBP-2	SCFsR	KPCI	PTN	C1s	0.878	0.852	1.73	0.902
		CD30Ligand	Kallikrein7	TCTP	C9				
66	IGFBP-2	CyclophilinA	ERBB1	Kallikrein7	Ubiquitin + 1	0.864	0.869	1.733	0.92
		SCFsR	PARC	CK-MB	FGF-17				
67	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	0.897	0.847	1.743	0.907
		sL-Selectin	KPCI	Kallikrein7	C1s				
68	CSK	KPCI	ERBB1	CK-MB	BLC	0.878	0.841	1.719	0.894
		SCFsR	PARC	Renin	Midkine				
69	IGFBP-2	SCFsR	GAPDH, liver	HSP90a	PTN	0.85	0.886	1.736	0.918
		FGF-17	PARC	Prothrombin	BMP-1				
70	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR	0.864	0.875	1.739	0.912
		HSP90a	Kallikrein7	CNDP1	Contactin-5				
71	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	0.883	0.849	1.732	0.899
		KPCI	IL-15Ra	CD30Ligand	Midkine				
72	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3	0.864	0.878	1.742	0.921
		SCFsR	LDH-H1	PARC	Kallikrein7				
73	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.887	0.844	1.731	0.893
		SCFsR	MEK1	LRIG3	UBE2N				
74	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	0.906	0.83	1.736	0.905
		sL-Selectin	KPCI	Kallikrein7	MIP-5				
75	CD30Ligand	PTN	ERBB1	TCTP	IGFBP-2	0.873	0.855	1.728	0.914
		Kallikrein7	SCFsR	GAPDH, liver	sL-Selectin				
76	CDK5-p35	IGFBP-2	HSP90a	PTN	SCFsR	0.878	0.855	1.733	0.91
		GAPDH, liver	CNDP1	LRIG3	Ubiquitin + 1				
77	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	0.864	0.869	1.733	0.91
		CD30Ligand	LRIG3	C9	CDK5-p35				
78	CD30Ligand	CyclophilinA	PTN	ERBB1	GAPDH, liver	0.864	0.852	1.716	0.915
		SCFsR	Kallikrein7	BLC	UBE2N				
79	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.864	0.872	1.736	0.92
		HSP90a	Kallikrein7	LRIG3	BMP-1				
80	PTN	C9	CSK	CD30Ligand	SCFsR	0.887	0.852	1.74	0.909
		KPCI	IGFBP-2	ERBB1	Kallikrein7				
81	PTN	LRIG3	ERBB1	HSP90a	Kallikrein7	0.854	0.886	1.741	0.915
		LDH-H1	PARC	CK-MB	Contactin-5				
82	CD30Ligand	CyclophilinA	PTN	ERBB1	GAPDH, liver	0.859	0.872	1.731	0.915
		IGFBP-2	Kallikrein7	IL-15Ra	SCFsR				
83	C1s	CSK	ERBB1	Kallikrein7	PTN	0.887	0.844	1.731	0.9
		SCFsR	GAPDH, liver	LDH-H1	MEK1				
84	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.883	0.852	1.735	0.9
		SCFsR	CDK5-p35	MIP-5	HSP90a				
85	CD30Ligand	KPCI	PTN	SCFsR	C9	0.887	0.841	1.728	0.898
		TCTP	Kallikrein7	IGFBP-2	BTK				
86	Kallikrein7	ERBB1	AMPM2	IGFBP-2	BTK	0.878	0.855	1.733	0.904
		SCFsR	C9	CDK5-p35	Ubiquitin + 1				
87	CSK	KPCI	ERBB1	CK-MB	BLC	0.878	0.838	1.716	0.899
		SCFsR	PARC	Renin	FGF-17				
88	LDH-H1	Kallikrein7	ERBB1	HSP90a	SCFsR	0.873	0.861	1.734	0.908
		LRIG3	BTK	PTN	BMP-1				
89	LRIG3	CNDP1	HSP90a	CK-MB	PTN	0.859	0.878	1.737	0.909
		GAPDH, liver	Kallikrein7	Endostatin	CD30Ligand				
90	IGFBP-2	KPCI	CD30Ligand	PTN	Contactin-5	0.892	0.847	1.739	0.903
		SCFsR	Kallikrein7	RAC1	C1s				
91	IGFBP-2	KPCI	CD30Ligand	SCFsR	PTN	0.897	0.849	1.746	0.902
		FYN	Kallikrein7	BTK	C9				
92	SCFsR	ERBB1	BTK	IGFBP-2	CDK5-p35	0.859	0.872	1.731	0.906
		Kallikrein7	AMPM2	IL-15Ra	PARC				
93	sL-Selectin	CyclophilinA	ERBB1	Kallikrein7	CD30Ligand	0.864	0.866	1.73	0.904
		PTN	GAPDH, liver	MEK1	C1s				
94	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.887	0.847	1.734	0.907
		SCFsR	MIP-5	RAC1	CK-MB				
95	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR	0.864	0.872	1.736	0.913
		HSP90a	Midkine	CD30Ligand	CDK5-p35				
96	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	0.878	0.849	1.727	0.906
		TCTP	PTN	LDH-H1	CNDP1				
97	CD30Ligand	Kallikrein7	KPCI	sL-Selectin	PTN	0.906	0.827	1.733	0.902
		SCFsR	BTK	C9	Ubiquitin + 1				
98	CK-MB	SCFsR	CSK	ERBB1	KPCI	0.878	0.838	1.716	0.897
		PARC	HSP90a	Prothrombin	BLC				
99	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	0.873	0.861	1.734	0.909
		PARC	RAC1	IGFBP-2	FGF-17				

TABLE 21-continued

100	IGFBP-2	KPCI SCFsR	CD30Ligand Kallikrein7	PTN BTK	Contactin-5 C9	0.883	0.855	1.738	0.906

Marker	Count	Marker	Count
SCFsR	91	LDH-H1	10
PTN	84	CSK	10
Kallikrein7	84	sL-Selectin	9
IGFBP-2	73	FGF-17	9
CD30Ligand	52	Endostatin	9
KPCI	40	Contactin-5	9
PARC	39	CNDP1	9
HSP90a	39	BMP-1	9
LRIG3	37	BLC	9
ERBB1	33	AMPM2	9
GAPDH, liver	25	Ubiquitin + 1	8
BTK	22	UBE2N	8
CK-MB	21	TCTP	8
CDK5-p35	20	Renin	8
C9	20	Midkine	8
RAC1	19	MIP-5	8
C1s	13	MEK1	8
Prothrombin	12	IL-15Ra	8
CyclophilinA	12	FYN	8

TABLE 22

100 Panels of 10 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers					Sensitivity	Specificity	Sens. + Spec.	AUC
1	PTN CD30Ligand	SCFsR LRIG3	AMPM2 C9	IGFBP-2 BTK	Kallikrein7 CK-MB	0.883	0.864	1.746	0.917
2	CSK SCFsR	KPCI PARC	ERBB1 Renin	CK-MB CDK5-p35	BLC HSP90a	0.892	0.844	1.736	0.901
3	PARC Prothrombin	SCFsR LRIG3	HSP90a RAC1	PTN BMP-1	IGFBP-2 Kallikrein7	0.887	0.866	1.754	0.92
4	BTK PTN	RAC1 SCFsR	ERBB1 sL-Selectin	Kallikrein7 C1s	IGFBP-2 PARC	0.873	0.886	1.76	0.925
5	LRIG3 GAPDH, liver	CNDP1 Kallikrein7	HSP90a Endostatin	CK-MB C1s	PTN BTK	0.878	0.875	1.753	0.914
6	BTK KPCI	IGFBP-2 HSP90a	PTN PARC	Kallikrein7 C9	SCFsR Contactin-5	0.892	0.861	1.753	0.906
7	Kallikrein7 PTN	CyclophilinA PARC	SCFsR Midkine	IGFBP-2 sL-Selectin	CD30Ligand RAC1	0.892	0.864	1.756	0.923
8	PTN Kallikrein7	RAC1 FGF-17	IGFBP-2 BTK	PARC Renin	SCFsR CD30Ligand	0.883	0.881	1.763	0.925
9	PARC CNDP1	GAPDH, liver LRIG3	SCFsR Kallikrein7	HSP90a IL-15Ra	PTN FYN	0.883	0.869	1.752	0.915
10	PTN Kallikrein7	RAC1 CD30Ligand	IGFBP-2 BTK	PARC Renin	SCFsR LDH-H1	0.887	0.869	1.757	0.92
11	IGFBP-2 BTK	SCFsR sL-Selectin	GAPDH, liver Kallikrein7	PTN PARC	CD30Ligand MEK1	0.854	0.892	1.747	0.914
12	IGFBP-2 PARC	SCFsR GAPDH, liver	RAC1 PTN	C1s MIP-5	Kallikrein7 LRIG3	0.869	0.878	1.746	0.923
13	C1s Prothrombin	SCFsR CD30Ligand	GAPDH, liver Kallikrein7	C9 TCTP	PTN LRIG3	0.892	0.852	1.744	0.91
14	IGFBP-2 Kallikrein7	SCFsR Prothrombin	KPCI CD30Ligand	PTN Renin	C1s UBE2N	0.906	0.847	1.753	0.905
15	CD30Ligand C9	Kallikrein7 IGFBP-2	KPCI BTK	sCFsR PTN	LRIG3 Ubiquitin + 1	0.901	0.849	1.751	0.906
16	BTK PTN	AMPM2 IGFBP-2	C9 CD30Ligand	SCFsR ERBB1	Kallikrein7 CDK5-p35	0.883	0.864	1.746	0.914
17	CyclophilinA IGFBP-2	HSP90a Kallikrein7	ERBB1 CDK5-p35	SCFsR CK-MB	PARC BLC	0.84	0.892	1.732	0.917
18	PTN Kallikrein7	RAC1 CD30Ligand	IGFBP-2 BTK	PARC Renin	SCFsR BMP-1	0.864	0.886	1.75	0.925
19	SCFsR Kallikrein7	ERBB1 CNDP1	CSK C9	PTN GAPDH, liver	IGFBP-2 Ubiquitin + 1	0.887	0.858	1.745	0.916
20	CD30Ligand BTK	IGFBP-2 ERBB1	PTN Kallikrein7	RAC1 Contactin-5	SCFsR PARC	0.859	0.886	1.746	0.923
21	Kallikrein7 CNDP1	SCFsR IGFBP-2	HSP90a Endostatin	PTN BTK	LRIG3 CK-MB	0.864	0.886	1.75	0.917
22	PTN Kallikrein7	RAC1 FGF-17	IGFBP-2 CD30Ligand	PARC GAPDH, liver	SCFsR sL-Selectin	0.883	0.869	1.752	0.926
23	PARC LRIG3	Kallikrein7 SCFsR	HSP90a C9	PTN UBE2N	IGFBP-2 FYN	0.883	0.869	1.752	0.919

TABLE 22-continued

24	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.897	0.847	1.743	0.9
	SCFsR	C9	CSK	Prothrombin	IL-15Ra				
25	LDH-H1	Kallikrein7	ERBB1	HSP90a	SCFsR	0.897	0.855	1.752	0.91
	LRIG3	BTK	PTN	GAPDH, liver	CNDP1				
26	CD30Ligand	CyclophilinA	PTN	ERBB1	GAPDH, liver	0.883	0.864	1.746	0.912
	SCFsR	Kallikrein7	MEK1	CDK5-p35	IGFBP-2				
27	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.897	0.849	1.746	0.906
	SCFsR	CDK5-p35	MIP-5	RAC1	LRIG3				
28	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand	0.873	0.878	1.751	0.924
	BTK	sL-Selectin	Kallikrein7	PARC	Midkine				
29	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.892	0.852	1.744	0.906
	SCFsR	C9	LRIG3	sL-Selectin	TCTP				
30	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	0.873	0.872	1.745	0.919
	CD30Ligand	Renin	BTK	CK-MB	PARC				
31	PTN	SCFsR	RAC1	HSP90a	IGFBP-2	0.864	0.866	1.73	0.918
	C1s	CDK5-p35	ERBB1	Kallikrein7	BLC				
32	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2	0.859	0.889	1.748	0.92
	LRIG3	sL-Selectin	Prothrombin	SCFsR	BMP-1				
33	IGFBP-2	KPCI	CD30Ligand	PTN	Contactin-5	0.887	0.858	1.745	0.905
	SCFsR	Kallikrein7	BTK	C9	Ubiquitin + 1				
34	CD30Ligand	SCFsR	KPCI	C9	BTK	0.901	0.847	1.748	0.904
	PTN	Kallikrein7	Prothrombin	Endostatin	IGFBP-2				
35	PARC	GAPDH, liver	HSP90a	PTN	IGFBP-2	0.869	0.881	1.749	0.919
	LRIG3	sL-Selectin	Prothrombin	FGF-17	SCFsR				
36	Kallikrein7	SCFsR	HSP90a	PTN	KPCI	0.897	0.855	1.752	0.906
	IGFBP-2	FYN	CD30Ligand	Renin	PARC				
37	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.887	0.855	1.742	0.906
	LRIG3	SCFsR	IL-15Ra	BTK	C9				
38	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.873	0.878	1.751	0.92
	CD30Ligand	GAPDH, liver	sL-Selectin	C1s	LDH-H1				
39	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3	0.873	0.869	1.743	0.909
	SCFsR	LDH-H1	Renin	Kallikrein7	MEK1				
40	CD30Ligand	KPCI	PTN	LRIG3	Kallikrein7	0.901	0.844	1.745	0.903
	MIP-5	SCFsR	IGFBP-2	GAPDH, liver	FGF-17				
41	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.878	0.872	1.75	0.922
	Kallikrein7	Midkine	CD30Ligand	BTK	Renin				
42	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.887	0.855	1.742	0.908
	SCFsR	C9	LRIG3	TCTP	Renin				
43	Kallikrein7	LRIG3	HSP90a	PTN	IGFBP-2	0.859	0.889	1.748	0.926
	CK-MB	SCFsR	UBE2N	PARC	Renin				
44	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	0.883	0.861	1.743	0.915
	CD30Ligand	Renin	BTK	Midkine	CK-MB				
45	CD30Ligand	SCFsR	ERBB1	CyclophilinA	PTN	0.864	0.861	1.725	0.916
	IGFBP-2	RAC1	Kallikrein7	BLC	sL-Selectin				
46	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.873	0.872	1.745	0.92
	HSP90a	Kallikrein7	LRIG3	FGF-17	BMP-1				
47	C1s	SCFsR	GAPDH, liver	C9	PTN	0.901	0.844	1.745	0.909
	Prothrombin	CD30Ligand	Ubiquitin + 1	Kallikrein7	CSK				
48	FGF-17	SCFsR	ERBB1	BTK	IGFBP-2	0.864	0.881	1.745	0.921
	Kallikrein7	PARC	RAC1	PTN	Contactin-5				
49	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.869	0.878	1.746	0.923
	Kallikrein7	CD30Ligand	BTK	Endostatin	sL-Selectin				
50	PTN	RAC1	IGFBP-2	PARC	sL-Selectin	0.873	0.875	1.748	0.922
	CD30Ligand	Kallikrein7	Midkine	FYN	SCFsR				
51	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.887	0.855	1.742	0.9
	LRIG3	SCFsR	FGF-17	CyclophilinA	IL-15Ra				
52	LDH-H1	Kallikrein7	ERBB1	HSP90a	SCFsR	0.892	0.849	1.741	0.901
	LRIG3	BTK	PTN	GAPDH, liver	MEK1				
53	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.892	0.852	1.744	0.904
	SCFsR	C9	CSK	MIP-5	CDK5-p35				
54	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	0.869	0.872	1.741	0.912
	PARC	ERBB1	LDH-H1	SCFsR	TCTP				
55	PTN	SCFsR	UBE2N	IGFBP-2	LRIG3	0.873	0.875	1.748	0.912
	LDH-H1	CD30Ligand	Kallikrein7	GAPDH, liver	FGF-17				
56	SCFsR	ERBB1	CSK	PTN	IGFBP-2	0.887	0.852	1.74	0.912
	Kallikrein7	CD30Ligand	C9	AMPM2	CDK5-p35				
57	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	0.864	0.861	1.725	0.918
	Kallikrein7	GAPDH, liver	ERBB1	BTK	BLC				
58	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.892	0.852	1.744	0.906
	SCFsR	CDK5-p35	C1s	RAC1	Contactin-5				
59	IGFBP-2	KPCI	CD30Ligand	SCFsR	LRIG3	0.883	0.864	1.746	0.908
	PTN	BTK	Kallikrein7	Endostatin	C9				
60	PTN	SCFsR	GAPDH, liver	HSP90a	C9	0.878	0.869	1.747	0.921
	LRIG3	IGFBP-2	FYN	Kallikrein7	PARC				
61	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.887	0.855	1.742	0.904
	SCFsR	C9	CSK	LRIG3	IL-15Ra				
62	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2	0.878	0.861	1.739	0.897
	Prothrombin	C1s	SCFsR	Renin	MEK1				
63	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.901	0.841	1.742	0.906
	SCFsR	C9	RAC1	BTK	MIP-5				

TABLE 22-continued

64	C1s	SCFsR	GAPDH, liver	C9	PTN	0.897	0.844	1.74	0.911
	Prothrombin	CD30Ligand	Kallikrein7	TCTP	Contactin-5				
65	C1s	SCFsR	GAPDH, liver	C9	PTN	0.901	0.847	1.748	0.913
	Prothrombin	CD30Ligand	Kallikrein7	UBE2N	FGF-17				
66	IGFBP-2	SCFsR	KPCI	PTN	C1s	0.892	0.858	1.75	0.903
	Kallikrein7	LRIG3	Prothrombin	CD30Ligand	Ubiquitin + 1				
67	IGFBP-2	SCFsR	KPCI	PTN	C1s	0.878	0.861	1.739	0.896
	Kallikrein7	LRIG3	Prothrombin	CD30Ligand	AMPM2				
68	Kallikrein7	GAPDH, liver	ERBB1	CD30Ligand	PTN	0.869	0.855	1.724	0.913
	FGF-17	CyclophilinA	SCFsR	LDH-H1	BLC				
69	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	0.864	0.881	1.745	0.915
	PARC	ERBB1	LDH-H1	SCFsR	UBE2N				
70	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	0.873	0.875	1.748	0.916
	FGF-17	GAPDH, liver	LRIG3	CNDP1	Kallikrein7				
71	CK-MB	ERBB1	HSP90a	PARC	BTK	0.873	0.872	1.745	0.915
	Kallikrein7	Endostatin	Prothrombin	LRIG3	SCFsR				
72	CD30Ligand	CyclophilinA	PTN	ERBB1	GAPDH, liver	0.883	0.864	1.746	0.915
	IGFBP-2	Kallikrein7	SCFsR	FYN	sL-Selectin				
73	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	0.873	0.866	1.74	0.918
	Kallikrein7	GAPDH, liver	ERBB1	BTK	IL-15Ra				
74	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3	0.883	0.855	1.738	0.894
	IGFBP-2	Prothrombin	KPCI	CD30Ligand	MEK1				
75	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3	0.892	0.849	1.741	0.908
	IGFBP-2	Prothrombin	KPCI	MIP-5	CK-MB				
76	PTN	KPCI	IGFBP-2	Prothrombin	HSP90a	0.883	0.866	1.749	0.904
	SCFsR	CD30Ligand	LRIG3	Midkine	PARC				
77	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	0.873	0.866	1.74	0.909
	TCTP	PTN	C9	LDH-H1	CD30Ligand				
78	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.901	0.847	1.748	0.905
	SCFsR	Ubiquitin + 1	BTK	C9	CDK5-p35				
79	CD30Ligand	Kallikrein7	KPCI	sL-Selectin	PTN	0.892	0.847	1.739	0.902
	SCFsR	BTK	C9	IGFBP-2	AMPM2				
80	CD30Ligand	SCFsR	ERBB1	CyclophilinA	PTN	0.859	0.861	1.72	0.916
	IGFBP-2	RAC1	Kallikrein7	BLC	Midkine				
81	CyclophilinA	HSP90a	ERBB1	SCFsR	PARC	0.854	0.889	1.744	0.918
	IGFBP-2	Kallikrein7	BMP-1	PTN	C1s				
82	CD30Ligand	Kallikrein7	ERBB1	BTK	PTN	0.887	0.861	1.748	0.918
	RAC1	SCFsR	GAPDH, liver	FGF-17	CNDP1				
83	IGFBP-2	CyclophilinA	ERBB1	Kallikrein7	Ubiquitin + 1	0.854	0.889	1.744	0.915
	SCFsR	PARC	CK-MB	CD30Ligand	Contactin-5				
84	CK-MB	Kallikrein7	HSP90a	PARC	CDK5-p35	0.873	0.872	1.745	0.918
	ERBB1	BTK	Endostatin	SCFsR	Prothrombin				
85	IGFBP-2	SCFsR	KPCI	PTN	C1s	0.911	0.835	1.746	0.905
	Kallikrein7	Prothrombin	CD30Ligand	Renin	FYN				
86	PARC	GAPDH, liver	SCFsR	HSP90a	PTN	0.887	0.852	1.74	0.915
	CNDP1	LRIG3	Kallikrein7	IL-15Ra	CyclophilinA				
87	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.878	0.858	1.736	0.898
	SCFsR	MEK1	LRIG3	Midkine	C9				
88	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	0.906	0.835	1.741	0.904
	Kallikrein7	KPCI	Renin	MIP-5	Prothrombin				
89	CD30Ligand	KPCI	PTN	SCFsR	C9	0.887	0.852	1.74	0.9
	TCTP	Kallikrein7	IGFBP-2	FGF-17	HSP90a				
90	PTN	SCFsR	UBE2N	IGFBP-2	LRIG3	0.892	0.855	1.747	0.911
	LDH-H1	CD30Ligand	GAPDH, liver	C1s	Prothrombin				
91	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	0.873	0.864	1.737	0.915
	CD30Ligand	LRIG3	C9	BTK	PARC				
92	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.85	0.869	1.719	0.921
	Kallikrein7	CD30Ligand	CyclophilinA	Renin	BLC				
93	LRIG3	CNDP1	HSP90a	CK-MB	PTN	0.869	0.875	1.744	0.915
	Kallikrein7	RAC1	Endostatin	BMP-1	Prothrombin				
94	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	0.892	0.852	1.744	0.907
	SCFsR	C9	CSK	sL-Selectin	LRIG3				
95	PTN	RAC1	IGFBP-2	PARC	SCFsR	0.869	0.875	1.744	0.922
	Kallikrein7	CD30Ligand	BTK	Renin	Contactin-5				
96	IGFBP-2	CyclophilinA	ERBB1	Kallikrein7	Ubiquitin + 1	0.859	0.886	1.746	0.918
	SCFsR	PARC	CK-MB	FYN	CD30Ligand				
97	CD30Ligand	IGFBP-2	PTN	CyclophilinA	SCFsR	0.887	0.852	1.74	0.905
	KPCI	LRIG3	Kallikrein7	C9	IL-15Ra				
98	CD30Ligand	IGFBP-2	PTN	CyclophilinA	SCFsR	0.878	0.858	1.736	0.898
	KPCI	LRIG3	Kallikrein7	C9	MEK1				
99	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2	0.873	0.866	1.74	0.923
	PTN	SCFsR	PARC	MIP-5	CDK5-p35				
100	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	0.887	0.852	1.74	0.91
	TCTP	PTN	C9	LDH-H1	FGF-17				

Marker	Count	Marker	Count
SCFsR	98	FGF-17	14
Kallikrein7	95	CK-MB	14
PTN	94	LDH-H1	12

TABLE 22-continued

IGFBP-2	81	CDK5-p35	12
CD30Ligand	69	CNDP1	9
LRIG3	45	Ubiquitin + 1	8
PARC	41	TCTP	8
BTK	35	Midkine	8
KPCI	34	MIP-5	8
C9	32	MEK1	8
RAC1	31	IL-15Ra	8
HSP90a	31	FYN	8
ERBB1	29	Endostatin	8
GAPDH, liver	27	Contactin-5	8
Prothrombin	22	CSK	8
Renin	17	BMP-1	8
C1s	17	BLC	8
sL-Selectin	15	AMPM2	8
CyclophilinA	15	UBE2N	7

TABLE 23

100 Panels of 11 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers							Sensitivity	Specificity	Sens. + Spec.	AUC
1	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	LRIG3	0.892	0.858	1.75	0.912
		C9	BTK	sL-Selectin	GAPDH, liver						
2	CSK	KPCI	ERBB1	CK-MB	BLC	SCFsR	PARC	0.892	0.847	1.739	0.9
		Renin	CDK5-p35	HSP90a	BTK						
3	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2	LRIG3	sL-Selectin	0.878	0.875	1.753	0.921
		Prothrombin	SCFsR	BMP-1	BTK						
4	LRIG3	CNDP1	HSP90a	CK-MB	PTN	GAPDH, liver	Kallikrein7	0.892	0.872	1.764	0.916
		Endostatin	C1s	sL-Selectin	BTK						
5	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s	RAC1	PARC	0.892	0.861	1.753	0.918
		C9	Kallikrein7	UBE2N	Contactin-5						
6	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	CD30Ligand	PTN	Renin	0.887	0.872	1.759	0.921
		HSP90a	PARC	CK-MB	LDH-H1						
7	LRIG3	CNDP1	HSP90a	CK-MB	PTN	GAPDH, liver	Kallikrein7	0.892	0.869	1.761	0.912
		Endostatin	FGF-17	BTK	sL-Selectin						
8	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2	PTN	SCFsR	0.878	0.886	1.764	0.922
		sL-Selectin	CD30Ligand	PARC	FYN						
9	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	C9	0.897	0.855	1.752	0.907
		CSK	LRIG3	IL-15Ra	sL-Selectin						
10	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3	SCFsR	LDH-H1	0.887	0.869	1.757	0.909
		Renin	Kallikrein7	BTK	MEK1						
11	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	GAPDH, liver	0.901	0.849	1.751	0.916
		Kallikrein7	Prothrombin	MIP-5	CDK5-p35						
12	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2	PTN	SCFsR	0.869	0.889	1.758	0.924
		PARC	Midkine	sL-Selectin	CD30Ligand						
13	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	PARC	ERBB1	0.878	0.872	1.75	0.912
		LDH-H1	SCFsR	TCTP	Endostatin						
14	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	KPCI	CD30Ligand	0.901	0.852	1.754	0.91
		Renin	C9	CDK5-p35	Ubiquitin + 1						
15	LRIG3	IGFBP-2	HSP90a	PARC	PTN	BTK	SCFsR	0.887	0.861	1.748	0.915
		Kallikrein7	CNDP1	AMPM2	Renin						
16	CSK	KPCI	ERBB1	CK-MB	BLC	SCFsR	PARC	0.897	0.841	1.738	0.896
		Renin	CDK5-p35	HSP90a	TCTP						
17	FGF-17	Kallikrein7	ERBB1	RAC1	C9	LDH-H1	SCFsR	0.873	0.878	1.751	0.915
		BTK	IGFBP-2	PARC	Contactin-5						
18	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	CD30Ligand	0.878	0.881	1.759	0.926
		CyclophilinA	Renin	C1s	FGF-17						
19	IGFBP-2	SCFsR	KPCI	PTN	C1s	Kallikrein7	Prothrombin	0.887	0.872	1.759	0.907
		CD30Ligand	C9	PARC	FYN						
20	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	CD30Ligand	0.873	0.875	1.748	0.925
		CyclophilinA	sL-Selectin	IL-15Ra	CK-MB						
21	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	GAPDH, liver	0.897	0.852	1.749	0.907
		Kallikrein7	Prothrombin	MIP-5	MEK1						
22	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	Midkine	0.873	0.884	1.757	0.923
		CD30Ligand	BTK	sL-Selectin	Endostatin						
23	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s	RAC1	PARC	0.892	0.869	1.761	0.923
		C9	Kallikrein7	UBE2N	CD30Ligand						
24	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	C9	0.906	0.847	1.753	0.908
		CDK5-p35	LRIG3	Ubiquitin + 1	BTK						
25	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	LRIG3	0.869	0.878	1.746	0.918
		C9	BTK	Endostatin	CK-MB						
26	CSK	KPCI	ERBB1	CK-MB	BLC	SCFsR	PARC	0.887	0.847	1.734	0.899
		Renin	CDK5-p35	HSP90a	CyclophilinA						
27	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	sL-Selectin	0.869	0.884	1.752	0.923
		FYN	C1s	Prothrombin	BMP-1						

TABLE 23-continued

28	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	BTK	0.864	0.886	1.75	0.921
		ERBB1	Kallikrein7	Contactin-5	PARC	Prothrombin				
29	CD30Ligand	IGFBP-2	PTN	CyclophilinA	SCFsR	KPCI	0.901	0.847	1.748	0.906
		LRIG3	Kallikrein7	C9	IL-15Ra	CDK5-p35				
30	CD30Ligand	Kallikrein7	KPCI	SCFsR	LRIG3	C9	0.887	0.861	1.748	0.9
		IGFBP-2	BTK	PTN	MEK1	Contactin-5				
31	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.897	0.852	1.749	0.909
		CDK5-p35	MIP-5	RAC1	LRIG3	C9				
32	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	CD30Ligand	PTN	0.901	0.855	1.757	0.912
		Renin	C1s	KPCI	CK-MB	Midkine				
33	IGFBP-2	SCFsR	KPCI	PTN	C1s	Kallikrein7	0.892	0.858	1.75	0.906
		Prothrombin	CD30Ligand	C9	PARC	TCTP				
34	CD30Ligand	Kallikrein7	KPCI	sL-Selectin	PTN	SCFsR	0.901	0.855	1.757	0.909
		BTK	C9	IGFBP-2	UBE2N	C1s				
35	BTK	GAPDH, liver	ERBB1	IGFBP-2	Kallikrein7	PTN	0.897	0.855	1.752	0.918
		C1s	SCFsR	CDK5-p35	Ubiquitin + 1	LDH-H1				
36	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.883	0.864	1.746	0.918
		LRIG3	C9	BTK	sL-Selectin	PARC				
37	PARC	SCFsR	HSP90a	PTN	IGFBP-2	Prothrombin	0.864	0.869	1.733	0.921
		LRIG3	RAC1	BMP-1	Kallikrein7	BLC				
38	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.883	0.875	1.758	0.918
		CD30Ligand	BTK	CNDP1	Renin	FYN				
39	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2	PTN	0.878	0.878	1.756	0.921
		SCFsR	PARC	LDH-H1	FGF-17	Midkine				
40	CD30Ligand	IGFBP-2	PTN	CyclophilinA	SCFsR	KPCI	0.897	0.849	1.746	0.908
		LRIG3	Kallikrein7	C9	IL-15Ra	sL-Selectin				
41	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	CD30Ligand	PTN	0.878	0.869	1.747	0.906
		Renin	C1s	LDH-H1	sL-Selectin	MEK1				
42	IGFBP-2	KPCI	CD30Ligand	PTN	Contactin-5	SCFsR	0.901	0.847	1.748	0.904
		Kallikrein7	RAC1	MIP-5	C1s	Prothrombin				
43	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.887	0.861	1.748	0.906
		C9	CDK5-p35	LRIG3	TCTP	Endostatin				
44	C1s	SCFsR	GAPDH, liver	C9	PTN	Prothrombin	0.883	0.872	1.755	0.92
		CD30Ligand	Kallikrein7	UBE2N	sL-Selectin	Endostatin				
45	IGFBP-2	SCFsR	KPCI	PTN	C1s	Kallikrein7	0.897	0.852	1.749	0.91
		LRIG3	Prothrombin	CD30Ligand	CK-MB	Ubiquitin + 1				
46	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.897	0.849	1.746	0.905
		LRIG3	C9	BTK	sL-Selectin	KPCI				
47	LRIG3	IGFBP-2	HSP90a	PARC	PTN	BTK	0.854	0.878	1.732	0.916
		SCFsR	Kallikrein7	ERBB1	LDH-H1	BLC				
48	PTN	RAC1	IGFBP-2	PARC	SCFsR	HSP90a	0.869	0.884	1.752	0.921
		Kallikrein7	LRIG3	BMP-1	Renin	FYN				
49	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.901	0.852	1.754	0.919
		GAPDH, liver	Kallikrein7	CNDP1	BTK	sL-Selectin				
50	IGFBP-2	SCFsR	KPCI	PTN	C1s	Kallikrein7	0.897	0.864	1.76	0.907
		Prothrombin	CD30Ligand	C9	CSK	PARC				
51	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.869	0.886	1.755	0.924
		FGF-17	CD30Ligand	GAPDH, liver	sL-Selectin	Endostatin				
52	PTN	SCFsR	RAC1	HSP90a	IGFBP-2	C1s	0.864	0.881	1.745	0.923
		CDK5-p35	ERBB1	Kallikrein7	PARC	IL-15Ra				
53	CD30Ligand	Kallikrein7	KPCI	SCFsR	LRIG3	C9	0.887	0.855	1.742	0.898
		IGFBP-2	BTK	PTN	MEK1	UBE2N				
54	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.901	0.847	1.748	0.914
		GAPDH, liver	Kallikrein7	Prothrombin	MIP-5	FGF-17				
55	PTN	RAC1	IGFBP-2	PARC	sL-Selectin	CD30Ligand	0.873	0.881	1.754	0.919
		Kallikrein7	Prothrombin	SCFsR	Midkine	Endostatin				
56	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.883	0.861	1.743	0.91
		C9	CDK5-p35	LRIG3	TCTP	Renin				
57	CD30Ligand	Kallikrein7	KPCI	SCFsR	LRIG3	C9	0.897	0.852	1.749	0.909
		IGFBP-2	BTK	PTN	Ubiquitin + 1	CNDP1				
58	BTK	AMPM2	C9	SCFsR	Kallikrein7	PTN	0.873	0.872	1.745	0.918
		IGFBP-2	CD30Ligand	ERBB1	CDK5-p35	PARC				
59	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.883	0.849	1.732	0.912
		LRIG3	C9	BTK	sL-Selectin	BLC				
60	PTN	RAC1	IGFBP-2	PARC	SCFsR	HSP90a	0.883	0.869	1.752	0.919
		Prothrombin	FGF-17	Kallikrein7	LRIG3	BMP-1				
61	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.915	0.841	1.756	0.906
		C9	CDK5-p35	CSK	Prothrombin	Renin				
62	CD30Ligand	SCFsR	ERBB1	CyclophilinA	PTN	IGFBP-2	0.883	0.866	1.749	0.92
		RAC1	Kallikrein7	Contactin-5	PARC	Prothrombin				
63	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR	HSP90a	0.878	0.881	1.759	0.922
		Kallikrein7	CD30Ligand	PARC	FYN	C9				
64	CyclophilinA	HSP90a	ERBB1	SCFsR	PARC	IGFBP-2	0.864	0.881	1.745	0.917
		Kallikrein7	CDK5-p35	sL-Selectin	CK-MB	IL-15Ra				
65	CD30Ligand	Kallikrein7	KPCI	SCFsR	LRIG3	C9	0.887	0.855	1.742	0.9
		IGFBP-2	BTK	PTN	MEK1	Ubiquitin + 1				
66	IGFBP-2	SCFsR	RAC1	C1s	Kallikrein7	PARC	0.878	0.869	1.747	0.923
		GAPDH, liver	PTN	MIP-5	LRIG3	Prothrombin				
67	FGF-17	SCFsR	ERBB1	BTK	IGFBP-2	Kallikrein7	0.873	0.878	1.751	0.922
		PARC	RAC1	sL-Selectin	Midkine	PTN				

TABLE 23-continued

68	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	TCTP	0.883	0.861	1.743	0.911
		PTN	C9	LDH-H1	CD30Ligand	Prothrombin				
69	CD30Ligand	sL-Selectin	GAPDH, liver	PTN	IGFBP-2	Kallikrein7	0.883	0.872	1.755	0.929
		PARC	SCFsR	UBE2N	C1s	CDK5-p35				
70	CSK	KPCI	ERBB1	CK-MB	BLC	SCFsR	0.883	0.849	1.732	0.903
		PARC	Renin	CDK5-p35	HSP90a	Prothrombin				
71	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	PARC	0.859	0.892	1.751	0.914
		ERBB1	LDH-H1	SCFsR	FYN	C9				
72	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.892	0.861	1.753	0.919
		GAPDH, liver	Kallikrein7	CNDP1	BTK	IGFBP-2				
73	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	KPCI	0.883	0.866	1.749	0.911
		CD30Ligand	Renin	CK-MB	HSP90a	Contactin-5				
74	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.892	0.852	1.744	0.905
		C9	RAC1	BTK	CDK5-p35	IL-15Ra				
75	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3	SCFsR	0.887	0.855	1.742	0.906
		LDH-H1	Renin	Kallikrein7	HSP90a	MEK1				
76	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s	RAC1	0.892	0.855	1.747	0.913
		CD30Ligand	Kallikrein7	LDH-H1	Prothrombin	MIP-5				
77	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand	BTK	0.873	0.878	1.751	0.921
		PARC	Kallikrein7	FYN	sL-Selectin	Midkine				
78	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.892	0.849	1.741	0.907
		C9	CDK5-p35	LRIG3	TCTP	sL-Selectin				
79	PTN	SCFsR	UBE2N	IGFBP-2	LRIG3	LDH-H1	0.878	0.875	1.753	0.919
		CD30Ligand	Kallikrein7	C9	Prothrombin	PARC				
80	IGFBP-2	KPCI	CD30Ligand	SCFsR	PTN	BTK	0.901	0.847	1.748	0.902
		Prothrombin	C9	Kallikrein7	Ubiquitin + 1	LRIG3				
81	BTK	AMPM2	C9	SCFsR	Kallikrein7	PTN	0.887	0.858	1.745	0.912
		IGFBP-2	CD30Ligand	ERBB1	CDK5-p35	CyclophilinA				
82	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	CyclophilinA	0.859	0.872	1.731	0.923
		PARC	PTN	CK-MB	GAPDH, liver	BLC				
83	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	PARC	0.873	0.878	1.751	0.917
		ERBB1	LDH-H1	SCFsR	UBE2N	CDK5-p35				
84	CD30Ligand	SCFsR	ERBB1	CyclophilinA	Kallikrein7	GAPDH, liver	0.883	0.869	1.752	0.918
		CDK5-p35	PTN	C1s	UBE2N	CNDP1				
85	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	CSK	0.873	0.875	1.748	0.916
		C9	PARC	sL-Selectin	PTN	CNDP1				
86	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s	UBE2N	0.887	0.861	1.748	0.914
		CD30Ligand	Kallikrein7	LDH-H1	Prothrombin	Contactin-5				
87	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	sL-Selectin	0.892	0.852	1.744	0.91
		KPCI	Kallikrein7	LRIG3	IL-15Ra	C9				
88	BTK	GAPDH, liver	ERBB1	CD30Ligand	PTN	SCFsR	0.878	0.864	1.742	0.913
		IGFBP-2	Kallikrein7	UBE2N	CDK5-p35	MEK1				
89	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.883	0.864	1.746	0.919
		GAPDH, liver	Kallikrein7	Prothrombin	MIP-5	sL-Selectin				
90	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin	SCFsR	0.873	0.878	1.751	0.919
		CK-MB	LDH-H1	PARC	Renin	Midkine				
91	IGFBP-2	SCFsR	KPCI	PTN	C1s	CD30Ligand	0.883	0.858	1.741	0.91
		Kallikrein7	TCTP	C9	sL-Selectin	PARC				
92	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.892	0.855	1.747	0.907
		Ubiquitin + 1	BTK	C9	FGF-17	LRIG3				
93	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.883	0.861	1.743	0.911
		LRIG3	C9	BTK	sL-Selectin	CNDP1				
94	CSK	KPCI	ERBB1	CK-MB	BLC	SCFsR	0.887	0.844	1.731	0.908
		PARC	Renin	CDK5-p35	HSP90a	PTN				
95	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.864	0.886	1.75	0.923
		CD30Ligand	BTK	CNDP1	BMP-1	Renin				
96	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	KPCI	0.887	0.861	1.748	0.908
		HSP90a	PARC	CDK5-p35	C9	Contactin-5				
97	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.883	0.875	1.758	0.919
		CD30Ligand	HSP90a	LRIG3	C9	FYN				
98	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	LRIG3	0.892	0.852	1.744	0.905
		SCFsR	IL-15Ra	BTK	C9	RAC1				
99	LDH-H1	Kallikrein7	ERBB1	HSP90a	SCFsR	LRIG3	0.892	0.849	1.741	0.904
		BTK	PTN	GAPDH, liver	MEK1	CDK5-p35				
100	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.897	0.849	1.746	0.908
		MIP-5	GAPDH, liver	C9	FYN	sL-Selectin				

Marker	Count	Marker	Count
SCFsR	98	LDH-H1	17
PTN	94	CK-MB	16
Kallikrein7	94	CyclophilinA	13
IGFBP-2	79	UBE2N	11
CD30Ligand	70	CNDP1	11
PARC	50	FYN	10
C9	50	MIP-5	9
LRIG3	45	MEK1	9
BTK	43	IL-15Ra	9
RAC1	37	FGF-17	9
KPCI	36	Endostatin	9

TABLE 23-continued

sL-Selectin	31	Contactin-5	9
HSP90a	29	CSK	9
C1s	28	BMP-1	9
ERBB1	27	BLC	9
Prothrombin	26	AMPM2	9
CDK5-p35	26	Ubiquitin + 1	8
GAPDH, liver	25	TCTP	8
Renin	20	Midkine	8

TABLE 24

100 Panels of 12 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers						Sensitivity	Specificity	Sens. + Spec.	AUC
1	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.883	0.878	1.76	0.922
	LRIG3	C9	BTK	PARC	CK-MB	C1s				
2	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	PARC	0.859	0.884	1.743	0.916
	ERBB1	LDH-H1	SCFsR	UBE2N	CDK5-p35	BLC				
3	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3	SCFsR	0.897	0.866	1.763	0.915
	LDH-H1	Renin	Kallikrein7	BTK	CNDP1	Prothrombin				
4	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	Kallikrein7	0.887	0.869	1.757	0.925
	LDH-H1	LRIG3	CK-MB	PARC	Renin	CSK				
5	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s	RAC1	0.906	0.855	1.761	0.913
	CD30Ligand	Kallikrein7	LDH-H1	Prothrombin	MIP-5	Contactin-5				
6	Kallikrein7	SCFsR	HSP90a	PTN	ERBB1	CyclophilinA	0.873	0.889	1.762	0.924
	IGFBP-2	CK-MB	PARC	LDH-H1	LRIG3	C1s				
7	C1s	SCFsR	GAPDH, liver	C9	PTN	Prothrombin	0.897	0.869	1.766	0.919
	CD30Ligand	Kallikrein7	UBE2N	sL-Selectin	Endostatin	FYN				
8	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.897	0.864	1.76	0.922
	FGF-17	CD30Ligand	LDH-H1	Renin	BTK	GAPDH, liver				
9	CD30Ligand	Kallikrein7	KPCI	sL-Selectin	PTN	SCFsR	0.897	0.858	1.755	0.908
	BTK	C9	IGFBP-2	UBE2N	LRIG3	IL-15Ra				
10	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	KPCI	0.911	0.847	1.757	0.901
	CD30Ligand	HSP90a	C9	Prothrombin	Renin	MEK1				
11	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2	LRIG3	0.883	0.881	1.763	0.92
	sL-Selectin	Prothrombin	SCFsR	BMP-1	BTK	Midkine				
12	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.897	0.855	1.752	0.91
	C9	CDK5-p35	LRIG3	TCTP	Renin	Ubiquitin + 1				
13	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.883	0.872	1.755	0.921
	LRIG3	C9	BTK	PARC	CK-MB	Midkine				
14	SCFsR	C9	UBE2N	CD30Ligand	PTN	KPCI	0.901	0.841	1.742	0.905
	Kallikrein7	IGFBP-2	Prothrombin	BTK	LRIG3	BLC				
15	IGFBP-2	SCFsR	KPCI	PTN	C1s	CD30Ligand	0.897	0.864	1.76	0.909
	Kallikrein7	RAC1	CNDP1	LRIG3	Endostatin	Prothrombin				
16	PTN	C9	CSK	CD30Ligand	SCFsR	GAPDH, liver	0.887	0.869	1.757	0.916
	Kallikrein7	LRIG3	IGFBP-2	Renin	FGF-17	Prothrombin				
17	CD30Ligand	SCFsR	KPCI	C9	BTK	PTN	0.906	0.855	1.761	0.91
	Kallikrein7	C1s	IGFBP-2	sL-Selectin	RAC1	Contactin-5				
18	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR	KPCI	0.901	0.861	1.762	0.909
	CD30Ligand	Renin	C9	CDK5-p35	CyclophilinA	LRIG3				
19	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3	SCFsR	0.883	0.878	1.76	0.916
	LDH-H1	Renin	Kallikrein7	C1s	FYN	Prothrombin				
20	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.897	0.858	1.755	0.91
	C9	CDK5-p35	LRIG3	BTK	IL-15Ra	sL-Selectin				
21	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3	SCFsR	0.873	0.881	1.754	0.91
	LDH-H1	Renin	Kallikrein7	C1s	Prothrombin	MEK1				
22	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.897	0.858	1.755	0.917
	GAPDH, liver	Kallikrein7	Prothrombin	MIP-5	sL-Selectin	FYN				
23	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.892	0.858	1.75	0.907
	C9	CDK5-p35	LRIG3	TCTP	Renin	BTK				
24	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s	RAC1	0.897	0.869	1.766	0.927
	PARC	C9	Kallikrein7	LRIG3	sL-Selectin	Ubiquitin + 1				
25	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.883	0.872	1.755	0.918
	LRIG3	C9	BTK	sL-Selectin	PARC	C1s				
26	IGFBP-2	KPCI	CD30Ligand	SCFsR	PTN	BTK	0.897	0.841	1.738	0.907
	Prothrombin	C9	Kallikrein7	Ubiquitin + 1	LRIG3	BLC				
27	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2	Prothrombin	0.915	0.858	1.773	0.908
	C1s	SCFsR	BMP-1	Renin	RAC1	CD30Ligand				
28	PTN	RAC1	IGFBP-2	PARC	SCFsR	HSP90a	0.901	0.858	1.759	0.919
	Prothrombin	FGF-17	C1s	GAPDH, liver	Kallikrein7	CNDP1				
29	PTN	C9	CSK	CD30Ligand	SCFsR	GAPDH, liver	0.901	0.855	1.757	0.917
	Kallikrein7	LRIG3	IGFBP-2	Renin	sL-Selectin	Prothrombin				
30	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2	LRIG3	0.887	0.869	1.757	0.918
	SCFsR	C9	UBE2N	RAC1	CD30Ligand	Contactin-5				
31	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	C1s	C9	0.883	0.878	1.76	0.922
	GAPDH, liver	PARC	PTN	LDH-H1	LRIG3	sL-Selectin				

TABLE 24-continued

32	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2	PTN	0.869	0.889	1.758	0.926
	SCFsR	PARC	C1s	CD30Ligand	sL-Selectin	Prothrombin				
33	Prothrombin	IGFBP-2	HSP90a	PTN	GAPDH, liver	SCFsR	0.887	0.872	1.759	0.92
	Kallikrein7	FGF-17	PARC	FYN	Endostatin	sL-Selectin				
34	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.901	0.852	1.754	0.908
	C9	CDK5-p35	CSK	LRIG3	IL-15Ra	sL-Selectin				
35	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2	Prothrombin	0.906	0.847	1.753	0.9
	C1s	SCFsR	Renin	BTK	C9	MEK1				
36	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.901	0.852	1.754	0.908
	C9	RAC1	BTK	MIP-5	LRIG3	CDK5-p35				
37	PTN	RAC1	IGFBP-2	PARC	sL-Selectin	CD30Ligand	0.878	0.881	1.759	0.919
	Kallikrein7	Prothrombin	SCFsR	FYN	Midkine	Endostatin				
38	IGFBP2	SCFsR	KPCI	PTN	C1s	Kallikrein7	0.887	0.861	1.748	0.907
	Prothrombin	CD30Ligand	C9	PARC	TCTP	LRIG3				
39	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.901	0.852	1.754	0.915
	LRIG3	C9	BTK	LDH-H1	Prothrombin	CK-MB				
40	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.869	0.866	1.735	0.924
	FGF-17	CD30Ligand	GAPDH, liver	Renin	CyclophilinA	BLC				
41	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2	Prothrombin	0.901	0.858	1.759	0.909
	C1s	SCFsR	BMP-1	Renin	BTK	CDK5-p35				
42	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.873	0.884	1.757	0.921
	CD30Ligand	FYN	Renin	BTK	BMP-1	CNDP1				
43	Kallikrein7	SCFsR	HSP90a	PTN	KPCI	CD30Ligand	0.897	0.858	1.755	0.91
	IGFBP-2	Renin	CDK5-p35	BTK	BMP-1	Contactin-5				
44	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2	PTN	0.873	0.884	1.757	0.926
	SCFsR	PARC	Midkine	sL-Selectin	C1s	CDK5-p35				
45	CD30Ligand	IGFBP-2	PTN	CyclophilinA	SCFsR	KPCI	0.901	0.852	1.754	0.907
	LRIG3	Kallikrein7	C9	IL-15Ra	sL-Selectin	BTK				
46	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.897	0.855	1.752	0.91
	GAPDH, liver	Kallikrein7	Prothrombin	LRIG3	sL-Selectin	MEK1				
47	IGFBP-2	KPCI	CD30Ligand	SCFsR	LRIG3	PTN	0.901	0.852	1.754	0.911
	UBE2N	Kallikrein7	C9	CDK5-p35	sL-Selectin	MIP-5				
48	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	TCTP	0.883	0.864	1.746	0.91
	PTN	C9	LDH-H1	CD30Ligand	Prothrombin	Contactin-5				
49	BTK	GAPDH, liver	C9	SCFsR	Kallikrein7	PARC	0.887	0.869	1.757	0.923
	IGFBP-2	PTN	CD30Ligand	LRIG3	Ubiquitin + 1	LDH-H1				
50	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.869	0.884	1.752	0.922
	LRIG3	C9	BTK	PARC	CK-MB	Endostatin				
51	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3	PARC	0.869	0.866	1.735	0.912
	ERBB1	LDH-H1	CSK	Endostatin	SCFsR	BLC				
52	CD30Ligand	SCFsR	RAC1	C9	PTN	LRIG3	0.887	0.869	1.757	0.914
	Kallikrein7	IGFBP-2	LDH-H1	BTK	Endostatin	CNDP1				
53	CD30Ligand	IGFBP-2	PTN	CyclophilinA	SCFsR	KPCI	0.901	0.852	1.754	0.909
	LRIG3	Kallikrein7	C9	IL-15Ra	sL-Selectin	CDK5-p35				
54	C1s	SCFsR	GAPDH, liver	C9	PTN	Prothrombin	0.887	0.864	1.751	0.916
	CD30Ligand	Kallikrein7	UBE2N	IGFBP-2	PARC	MEK1				
55	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.906	0.847	1.753	0.906
	CDK5-p35	C1s	RAC1	MIP-5	C9	FYN				
56	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	CDK5-p35	0.897	0.861	1.758	0.921
	Kallikrein7	PARC	FYN	Renin	HSP90a	Midkine				
57	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	TCTP	0.897	0.849	1.746	0.904
	PTN	C9	LDH-H1	CD30Ligand	Prothrombin	KPCI				
58	IGFBP-2	KPCI	CD30Ligand	SCFsR	Kallikrein7	CSK	0.901	0.855	1.757	0.911
	PTN	C1s	C9	CDK5-p35	Ubiquitin + 1	Renin				
59	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.883	0.869	1.752	0.92
	LRIG3	C9	BTK	sL-Selectin	Renin	PARC				
60	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.859	0.875	1.734	0.921
	CD30Ligand	CyclophilinA	Renin	C1s	Midkine	BLC				
61	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.892	0.864	1.756	0.924
	FGF-17	BTK	Renin	CD30Ligand	Ubiquitin + 1	CNDP1				
62	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.878	0.875	1.753	0.924
	CD30Ligand	CyclophilinA	sL-Selectin	ERBB1	CDK5-p35	Contactin-5				
63	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR	sL-Selectin	0.897	0.855	1.752	0.908
	KPCI	Kallikrein7	LRIG3	IL-15Ra	C9	BTK				
64	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.878	0.872	1.75	0.912
	CD30Ligand	C1s	LDH-H1	C9	Prothrombin	MEK1				
65	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.906	0.847	1.753	0.909
	C9	RAC1	BTK	MIP-5	sL-Selectin	C1s				
66	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.887	0.858	1.745	0.904
	C9	CDK5-p35	LRIG3	TCTP	Endostatin	FYN				
67	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.883	0.869	1.752	0.917
	LRIG3	C9	BTK	sL-Selectin	CNDP1	PARC				
68	BTK	GAPDH, liver	C9	SCFsR	Kallikrein7	PARC	0.836	0.898	1.733	0.924
	IGFBP-2	PTN	CD30Ligand	LRIG3	CK-MB	BLC				
69	IGFBP-2	KPCI	CD30Ligand	SCFsR	Kallikrein7	CSK	0.901	0.855	1.757	0.915
	PTN	Renin	CK-MB	C1s	Prothrombin	PARC				
70	PTN	RAC1	IGFBP-2	PARC	SCFsR	HSP90a	0.878	0.875	1.753	0.922
	Kallikrein7	LRIG3	BMP-1	Renin	Prothrombin	Contactin-5				
71	PTN	RAC1	IGFBP-2	PARC	SCFsR	HSP90a	0.901	0.855	1.757	0.92
	Prothrombin	FGF-17	C1s	GAPDH, liver	Kallikrein7	C9				

TABLE 24-continued

72	IGFBP-2	SCFsR	KPCI	PTN	C1s	Kallikrein7	0.892	0.858	1.75	0.906
	Prothrombin	CD30Ligand	C9	CSK	PARC	IL-15Ra				
73	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.897	0.852	1.749	0.904
	Ubiquitin + 1	sL-Selectin	C9	BTK	LRIG3	MEK1				
74	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.883	0.869	1.752	0.923
	FGF-17	CD30Ligand	GAPDH, liver	Renin	MIP-5	FYN				
75	PTN	RAC1	IGFBP-2	PARC	SCFsR	HSP90a	0.873	0.884	1.757	0.919
	Kallikrein7	LRIG3	BMP-1	Renin	Midkine	CD30Ligand				
76	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.883	0.861	1.743	0.909
	C9	CDK5-p35	LRIG3	TCTP	sL-Selectin	C1s				
77	IGFBP-2	SCFsR	KPCI	PTN	C1s	CD30Ligand	0.897	0.855	1.752	0.908
	Kallikrein7	AMPM2	BTK	Prothrombin	Renin	CK-MB				
78	LDH-H1	Kallikrein7	ERBB1	HSP90a	SCFsR	LRIG3	0.864	0.869	1.733	0.915
	BTK	PTN	GAPDH, liver	CNDP1	PARC	BLC				
79	IGFBP-2	SCFsR	KPCI	PTN	C1s	CD30Ligand	0.906	0.847	1.753	0.906
	Kallikrein7	RAC1	CNDP1	LRIG3	Prothrombin	Contactin-5				
80	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2	SCFsR	0.883	0.866	1.749	0.908
	C9	CDK5-p35	LRIG3	BTK	IL-15Ra	Contactin-5				
81	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.873	0.875	1.748	0.915
	CD30Ligand	BTK	Renin	C9	LDH-H1	MEK1				
82	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.897	0.855	1.752	0.918
	GAPDH, liver	Kallikrein7	Prothrombin	MIP-5	ERBB1	CyclophilinA				
83	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.878	0.878	1.756	0.926
	CD30Ligand	CyclophilinA	sL-Selectin	C9	C1s	Midkine				
84	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	TCTP	0.883	0.861	1.743	0.911
	PTN	C9	LDH-H1	CD30Ligand	Prothrombin	Endostatin				
85	CD30Ligand	sL-Selectin	GAPDH, liver	PTN	IGFBP-2	Kallikrein7	0.892	0.872	1.764	0.924
	PARC	SCFsR	UBE2N	LRIG3	C9	HSP90a				
86	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3	IGFBP-2	0.892	0.864	1.756	0.92
	Prothrombin	PARC	GAPDH, liver	C1s	CDK5-p35	Ubiquitin + 1				
87	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.873	0.878	1.751	0.916
	LRIG3	C9	BTK	PARC	FGF-17	Endostatin				
88	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s	RAC1	0.883	0.847	1.729	0.917
	CD30Ligand	Kallikrein7	LDH-H1	sL-Selectin	Prothrombin	BLC				
89	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2	Prothrombin	0.911	0.844	1.755	0.907
	C1s	SCFsR	BMP-1	Renin	CDK5-p35	CSK				
90	PTN	C9	CSK	CD30Ligand	SCFsR	GAPDH, liver	0.883	0.866	1.749	0.916
	Kallikrein7	LRIG3	IGFBP-2	Renin	Prothrombin	IL-15Ra				
91	CD30Ligand	Kallikrein7	KPCI	SCFsR	LRIG3	C9	0.901	0.847	1.748	0.902
	IGFBP-2	BTK	PTN	MEK1	Ubiquitin + 1	CDK5-p35				
92	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.911	0.841	1.752	0.915
	GAPDH, liver	Kallikrein7	Prothrombin	MIP-5	CDK5-p35	Midkine				
93	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7	TCTP	0.897	0.847	1.743	0.91
	PTN	C9	LDH-H1	CD30Ligand	Prothrombin	GAPDH, liver				
94	SCFsR	C9	UBE2N	C1s	PTN	RAC1	0.901	0.861	1.762	0.927
	CD30Ligand	IGFBP-2	Kallikrein7	GAPDH, liver	sL-Selectin	PARC				
95	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.901	0.849	1.751	0.91
	LRIG3	C9	BTK	LDH-H1	Prothrombin	sL-Selectin				
96	LDH-H1	SCFsR	HSP90a	PTN	ERBB1	PARC	0.845	0.884	1.729	0.923
	LRIG3	Kallikrein7	CK-MB	UBE2N	IGFBP-2	BLC				
97	CD30Ligand	SCFsR	RAC1	C9	PTN	C1s	0.892	0.864	1.756	0.919
	GAPDH, liver	Kallikrein7	CNDP1	BTK	sL-Selectin	FGF-17				
98	PTN	RAC1	IGFBP-2	PARC	SCFsR	Kallikrein7	0.883	0.869	1.752	0.922
	CD30Ligand	CyclophilinA	sL-Selectin	ERBB1	Prothrombin	Contactin-5				
99	IGFBP-2	KPCI	CD30Ligand	SCFsR	LRIG3	PTN	0.897	0.852	1.749	0.91
	UBE2N	Kallikrein7	C9	CDK5-p35	sL-Selectin	IL-15Ra				
100	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7	CD30Ligand	0.878	0.869	1.747	0.911
	LRIG3	C9	BTK	sL-Selectin	PARC	MEK1				

Marker	Count	Marker	Count
SCFsR	100	ERBB1	14
PTN	100	UBE2N	11
Kallikrein7	100	CyclophilinA	11
IGFBP-2	87	AMPM2	11
CD30Ligand	83	MEK1	10
C9	63	IL-15Ra	10
LRIG3	60	FYN	10
PARC	47	FGF-17	10
Prothrombin	43	Endostatin	10
RAC1	42	Contactin-5	10
BTK	42	CSK	10
C1s	40	CNDP1	10
KPCI	36	CK-MB	10
sL-Selectin	35	BMP-1	10
Renin	30	BLC	10
GAPDH, liver	27	Ubiquitin + 1	9
HSP90a	25	TCTP	9
CDK5-p35	24	Midkine	9
LDH-H1	23	MIP-5	9

TABLE 25

100 Panels of 13 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers				
1	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	sL-Selectin	PARC
2	PTN	RAC1	IGFBP-2	PARC	SCFsR
		sL-Selectin	C1s	LDH-H1	Prothrombin
3	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
		SCFsR	BMP-1	Renin	RAC1
4	PTN	RAC1	IGFBP-2	PARC	SCFsR
		CyclophilinA	Renin	C1s	CK-MB
5	CD30Ligand	SCFsR	RAC1	C9	PTN
		Kallikrein7	CNDP1	BTK	sL-Selectin
6	IGFBP-2	KPCI	CD30Ligand	SCFsR	Kallikrein7
		Renin	CK-MB	C1s	Prothrombin
7	CD30Ligand	C9	GAPDH, liver	SCFsR	PTN
		sL-Selectin	Kallikrein7	UBE2N	Endostatin
8	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2
		sL-Selectin	C1s	PARC	C9
9	PTN	LRIG3	CD30Ligand	GAPDH, liver	PARC
		Prothrombin	IGFBP-2	RAC1	C9
10	PTN	RAC1	IGFBP-2	PARC	SCFsR
		CD30Ligand	GAPDH, liver	Renin	BTK
11	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
		SCFsR	BMP-1	Renin	RAC1
12	CD30Ligand	SCFsR	RAC1	C9	PTN
		Kallikrein7	Prothrombin	MIP-5	ERBB1
13	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
		C9	LDH-H1	CD30Ligand	Prothrombin
14	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand
		Kallikrein7	PARC	C1s	C9
15	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		BTK	Midkine	CK-MB	PARC
16	PTN	RAC1	IGFBP-2	PARC	SCFsR
		CD30Ligand	GAPDH, liver	Renin	CyclophilinA
17	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
		Prothrombin	C1s	SCFsR	CyclophilinA
18	CD30Ligand	SCFsR	RAC1	C9	PTN
		Kallikrein7	CNDP1	BTK	sL-Selectin
19	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		CDK5-p35	CSK	Prothrombin	Renin
20	LRIG3	CNDP1	HSP90a	CK-MB	PTN
		Endostatin	FGF-17	BTK	sL-Selectin
21	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
		Kallikrein7	LRIG3	IL-15Ra	C9
22	CD30Ligand	IGFBP-2	PTN	GAPDH, liver	FYN
		C9	C1s	Kallikrein7	Prothrombin
23	CD30Ligand	SCFsR	RAC1	C9	PTN
		Kallikrein7	Prothrombin	MIP-5	ERBB1
24	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
		C9	LDH-H1	CD30Ligand	Prothrombin
25	CD30Ligand	sL-Selectin	GAPDH, liver	PTN	IGFBP-2
		SCFsR	UBE2N	LRIG3	C9
26	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	PARC	CK-MB
27	PTN	RAC1	IGFBP-2	PARC	SCFsR
		LRIG3	C1s	BMP-1	CDK5-p35
28	PTN	C9	CSK	CD30Ligand	SCFsR
		LRIG3	IGFBP-2	Renin	CDK5-p35
29	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR
		PARC	Renin	CD30Ligand	BMP-1
30	CD30Ligand	Kallikrein7	KPCI	sL-Selectin	PTN
		C9	IGFBP-2	UBE2N	LRIG3
31	PTN	RAC1	IGFBP-2	PARC	SCFsR
		LRIG3	BMP-1	Renin	Prothrombin
32	SCFsR	C9	UBE2N	C1s	PTN
		IGFBP-2	Kallikrein7	PARC	Prothrombin
33	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		RAC1	BTK	MIP-5	LRIG3
34	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
		C9	LDH-H1	CD30Ligand	Prothrombin
35	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	PARC	CK-MB
36	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand
		PARC	Kallikrein7	CK-MB	C1s
37	SCFsR	ERBB1	CSK	PTN	IGFBP-2
		C9	GAPDH, liver	Ubiquitin + 1	FGF-17
38	PTN	RAC1	IGFBP-2	PARC	SCFsR
		BTK	Endostatin	C9	Prothrombin

TABLE 25-continued

39	PTN	C9	CSK	CD30Ligand	SCFsR
		LRIG3	IGFBP-2	Renin	Prothrombin
40	PTN	RAC1	IGFBP-2	PARC	SCFsR
		LRIG3	C1s	Prothrombin	sL-Selectin
41	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		RAC1	BTK	MIP-5	sL-Selectin
42	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
		SCFsR	BMP-1	Renin	RAC1
43	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	sL-Selectin	PARC
44	CD30Ligand	SCFsR	ERBB1	CyclophilinA	PTN
		Kallikrein7	PARC	LDH-H1	Prothrombin
45	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
		SCFsR	CD30Ligand	CK-MB	Renin
46	LRIG3	CNDP1	HSP90a	CK-MB	PTN
		Endostatin	C1s	sL-Selectin	FGF-17
47	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		C1s	RAC1	C9	LRIG3
48	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		LRIG3	sL-Selectin	BTK	HSP90a
49	PTN	RAC1	IGFBP-2	PARC	SCFsR
		GAPDH, liver	C1s	LRIG3	LDH-H1
50	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
		LRIG3	CK-MB	PARC	Renin
51	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
		C9	UBE2N	RAC1	C1s
52	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	sL-Selectin	Renin
53	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
		LRIG3	CK-MB	PARC	Renin
54	PTN	RAC1	IGFBP-2	PARC	SCFsR
		HSP90a	LRIG3	C9	FYN
55	CD30Ligand	SCFsR	RAC1	C9	PTN
		Kallikrein7	CNDP1	BTK	sL-Selectin
56	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		sL-Selectin	C9	BTK	LRIG3
57	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	sL-Selectin	PARC
58	PTN	C9	CSK	CD30Ligand	SCFsR
		LRIG3	IGFBP-2	Renin	Prothrombin
59	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
		Renin	Kallikrein7	HSP90a	Midkine
60	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
		C9	LDH-H1	CD30Ligand	Prothrombin
61	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand
		Kallikrein7	PARC	C1s	C9
62	IGFBP-2	SCFsR	KPCI	PTN	C1s
		CD30Ligand	Renin	RAC1	HSP90a
63	SCFsR	C9	UBE2N	CD30Ligand	PTN
		IGFBP-2	Prothrombin	BTK	C1s
64	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		CDK5-p35	CyclophilinA	LRIG3	C1s
65	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand
		PARC	Kallikrein7	CK-MB	C1s
66	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
		Kallikrein7	LDH-H1	CDK5-p35	Prothrombin
67	PTN	RAC1	IGFBP-2	PARC	SCFsR
		CyclophilinA	sL-Selectin	C9	C1s
68	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
		C9	LDH-H1	CD30Ligand	Prothrombin
69	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	PARC	FGF-17
70	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	CD30Ligand
		LDH-H1	LRIG3	CK-MB	PARC
71	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
		C9	BTK	sL-Selectin	CNDP1
72	IGFBP-2	KPCI	CD30Ligand	SCFsR	Kallikrein7
		Renin	CK-MB	C1s	Prothrombin
73	BTK	GAPDH, liver	C9	SCFsR	Kallikrein7
		PTN	CD30Ligand	RAC1	Contactin-5
74	PTN	RAC1	IGFBP-2	PARC	SCFsR
		LRIG3	C9	C1s	Prothrombin
75	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR
		PARC	Renin	CD30Ligand	LRIG3
76	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
		Kallikrein7	LDH-H1	Prothrombin	Renin
77	Kallikrein7	LRIG3	HSP90a	PTN	IGFBP-2
		UBE2N	PARC	Renin	CD30Ligand
78	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		CDK5-p35	LRIG3	TCTP	Renin

TABLE 25-continued

79	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	sL-Selectin	Renin
80	BTK	GAPDH, liver	ERBB1	IGFBP-2	Kallikrein7
		SCFsR	CDK5-p35	PARC	RAC1
81	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
		Renin	Kallikrein7	BTK	CNDP1
82	Kallikrein7	BMP-1	HSP90a	PTN	LRIG3
		LDH-H1	CSK	Endostatin	SCFsR
83	PTN	RAC1	IGFBP-2	PARC	SCFsR
		LRIG3	BMP-1	Renin	Midkine
84	PTN	RAC1	IGFBP-2	PARC	SCFsR
		FGF-17	Kallikrein7	LRIG3	C9
85	C1s	SCFsR	GAPDH, liver	C9	PTN
		Kallikrein7	UBE2N	IGFBP-2	PARC
86	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
		RAC1	BTK	MIP-5	sL-Selectin
87	PTN	RAC1	IGFBP-2	PARC	SCFsR
		LRIG3	BMP-1	Renin	Midkine
88	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
		C9	BTK	sL-Selectin	CNDP1
89	IGFBP-2	SCFsR	KPCI	PTN	C1s
		CD30Ligand	C9	CyclophilinA	sL-Selectin
90	LDH-H1	SCFsR	HSP90a	PTN	ERBB1
		Kallikrein7	CK-MB	CSK	C1s
91	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
		C9	Kallikrein7	LRIG3	sL-Selectin
92	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
		LRIG3	LDH-H1	Prothrombin	Kallikrein7
93	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3
		PARC	FYN	C1s	RAC1
94	IGFBP-2	KPCI	CD30Ligand	SCFsR	LRIG3
		Kallikrein7	C9	CDK5-p35	sL-Selectin
95	PTN	KPCI	IGFBP-2	Prothrombin	HSP90a
		Kallikrein7	CD30Ligand	FYN	C9
96	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR
		RAC1	PARC	sL-Selectin	C9
97	CD30Ligand	KPCI	PTN	SCFsR	HSP90a
		IGFBP-2	CK-MB	Renin	Kallikrein7
98	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
		C9	BTK	sL-Selectin	Renin
99	LDH-H1	SCFsR	HSP90a	PTN	ERBB1
		Kallikrein7	CK-MB	UBE2N	IGFBP-2
100	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin
		LDH-H1	PARC	Renin	C1s

	Biomarkers		Sensitivity	Specificity	Sens. + Spec.	AUC
1	CD30Ligand	LRIG3	0.887	0.875	1.762	0.919
	CDK5-p35	C1s				
2	CD30Ligand	GAPDH, liver	0.883	0.869	1.752	0.923
	Kallikrein7	BLC				
3	Prothrombin	C1s	0.915	0.849	1.765	0.907
	CD30Ligand	FYN				
4	Kallikrein7	CD30Ligand	0.887	0.881	1.768	0.926
	Midkine	LDH-H1				
5	C1s	GAPDH, liver	0.906	0.861	1.767	0.917
	Prothrombin	LRIG3				
6	CSK	PTN	0.901	0.858	1.759	0.915
	PARC	Midkine				
7	CyclophilinA	C1s	0.901	0.861	1.762	0.916
	Prothrombin	Contactin-5				
8	PTN	SCFsR	0.897	0.875	1.772	0.925
	HSP90a	LRIG3				
9	HSP90a	SCFsR	0.901	0.866	1.768	0.92
	Kallikrein7	FGF-17				
10	Kallikrein7	FGF-17	0.887	0.869	1.757	0.921
	Prothrombin	IL-15Ra				
11	Prothrombin	C1s	0.901	0.858	1.759	0.902
	MEK1	CD30Ligand				
12	C1s	GAPDH, liver	0.911	0.849	1.76	0.916
	FYN	CyclophilinA				
13	TCTP	PTN	0.897	0.852	1.749	0.906
	KPCI	IGFBP-2				
14	BTK	sL-Selectin	0.901	0.861	1.762	0.924
	Ubiquitin + 1	LDH-H1				
15	CD30Ligand	Renin	0.883	0.878	1.76	0.92
	C1s	LRIG3				
16	Kallikrein7	FGF-17	0.873	0.872	1.745	0.927
	C1s	BLC				

TABLE 25-continued

17	LRIG3 C9	sL-Selectin CDK5-p35	0.897	0.875	1.772	0.922
18	C1s Prothrombin	GAPDH, liver Renin	0.915	0.849	1.765	0.92
19	SCFsR C1s	C9 CK-MB	0.906	0.852	1.758	0.916
20	GAPDH, liver PARC	Kallikrein7 Contactin-5	0.883	0.878	1.76	0.918
21	sL-Selectin CDK5-p35	KPCI FYN	0.906	0.849	1.756	0.909
22	SCFsR PARC	RAC1 MEK1	0.901	0.858	1.759	0.915
23	C1s CyclophilinA	GAPDH, liver PARC	0.901	0.855	1.757	0.922
24	TCTP KPCI	PTN Ubiquitin + 1	0.906	0.841	1.747	0.902
25	Kallikrein7 RAC1	PARC C1s	0.901	0.875	1.776	0.928
26	CD30Ligand FGF-17	LRIG3 Midkine	0.887	0.872	1.759	0.921
27	HSP90a Prothrombin	Kallikrein7 BLC	0.864	0.881	1.745	0.921
28	GAPDH, liver C1s	Kallikrein7 Prothrombin	0.883	0.875	1.758	0.918
29	KPCI Prothrombin	HSP90a Contactin-5	0.892	0.866	1.758	0.911
30	SCFsR Endostatin	BTK CDK5-p35	0.906	0.855	1.761	0.911
31	HSP90a IL-15Ra	Kallikrein7 CDK5-p35	0.878	0.875	1.753	0.923
32	RAC1 Ubiquitin + 1	CD30Ligand MEK1	0.906	0.849	1.756	0.912
33	SCFsR CDK5-p35	C9 CNDP1	0.901	0.855	1.757	0.91
34	TCTP KPCI	PTN BMP-1	0.897	0.849	1.746	0.905
35	CD30Ligand Midkine	LRIG3 FYN	0.887	0.872	1.759	0.92
36	BTK Ubiquitin + 1	Renin BLC	0.869	0.875	1.744	0.927
37	Kallikrein7 LDH-H1	CNDP1 Contactin-5	0.897	0.861	1.758	0.916
38	Kallikrein7 sL-Selectin	CD30Ligand LDH-H1	0.887	0.872	1.759	0.92
39	GAPDH, liver IL-15Ra	Kallikrein7 CDK5-p35	0.878	0.875	1.753	0.917
40	HSP90a C9	Kallikrein7 MEK1	0.883	0.872	1.755	0.915
41	SCFsR Prothrombin	C9 LRIG3	0.911	0.844	1.755	0.909
42	Prothrombin CD30Ligand	C1s TCTP	0.911	0.835	1.746	0.904
43	CD30Ligand C1s	LRIG3 CK-MB	0.887	0.872	1.759	0.924
44	IGFBP-2 CK-MB	RAC1 BLC	0.859	0.884	1.743	0.925
45	Prothrombin BTK	C1s Contactin-5	0.892	0.866	1.758	0.912
46	Kallikrein7 IGFBP-2	RAC1 SCFsR	0.878	0.881	1.759	0.923
47	SCFsR IL-15Ra	CDK5-p35 sL-Selectin	0.892	0.861	1.753	0.912
48	SCFsR Prothrombin	C9 MEK1	0.901	0.852	1.754	0.901
49	CD30Ligand Kallikrein7	Prothrombin MIP-5	0.892	0.861	1.753	0.918
50	Kallikrein7 C1s	LDH-H1 TCTP	0.873	0.872	1.745	0.925
51	LRIG3 sL-Selectin	SCFsR Prothrombin	0.901	0.866	1.768	0.923
52	CD30Ligand Prothrombin	LRIG3 CK-MB	0.901	0.858	1.759	0.92
53	Kallikrein7 CSK	LDH-H1 BLC	0.878	0.864	1.742	0.924
54	Kallikrein7 Contactin-5	CD30Ligand UBE2N	0.897	0.861	1.758	0.916
55	C1s Endostatin	GAPDH, liver LRIG3	0.892	0.866	1.758	0.922
56	SCFsR CDK5-p35	Ubiquitin + 1 IL-15Ra	0.906	0.847	1.753	0.91

TABLE 25-continued

57	CD30Ligand CDK5-p35	LRIG3 MEK1	0.878	0.875	1.753	0.912
58	GAPDH, liver MIP-5	Kallikrein7 sL-Selectin	0.892	0.861	1.753	0.918
59	SCFsR CK-MB	LDH-H1 PARC	0.892	0.872	1.764	0.923
60	TCTP KPCI	PTN PARC	0.887	0.858	1.745	0.908
61	BTK FYN	sL-Selectin BLC	0.845	0.895	1.74	0.92
62	Kallikrein7 Contactin-5	Prothrombin BMP-1	0.897	0.861	1.758	0.908
63	KPCI sL-Selectin	Kallikrein7 Endostatin	0.906	0.852	1.758	0.909
64	SCFsR IL-15Ra	C9 sL-Selectin	0.897	0.855	1.752	0.91
65	BTK Ubiquitin + 1	Renin MEK1	0.873	0.878	1.751	0.922
66	RAC1 MIP-5	CD30Ligand LRIG3	0.897	0.855	1.752	0.915
67	Kallikrein7 Midkine	CD30Ligand CK-MB	0.869	0.895	1.763	0.931
68	TCTP KPCI	PTN MIP-5	0.901	0.844	1.745	0.905
69	CD30Ligand sL-Selectin	LRIG3 Renin	0.883	0.875	1.758	0.92
70	PTN HSP90a	Renin BLC	0.859	0.881	1.74	0.922
71	LRIG3 C1s	SCFsR GAPDH, liver	0.878	0.886	1.764	0.923
72	CSK PARC	PTN Ubiquitin + 1	0.901	0.855	1.757	0.913
73	PARC sL-Selectin	IGFBP-2 Ubiquitin + 1	0.911	0.847	1.757	0.924
74	HSP90a Endostatin	Kallikrein7 FYN	0.883	0.875	1.758	0.922
75	KPCI BMP-1	HSP90a IL-15Ra	0.887	0.864	1.751	0.91
76	RAC1 LRIG3	CD30Ligand MEK1	0.887	0.864	1.751	0.912
77	CK-MB Midkine	SCFsR LDH-H1	0.883	0.881	1.763	0.921
78	SCFsR Ubiquitin + 1	C9 IL-15Ra	0.892	0.852	1.744	0.908
79	CD30Ligand Prothrombin	LRIG3 PARC	0.897	0.861	1.758	0.919
80	PTN sL-Selectin	C1s BLC	0.873	0.866	1.74	0.928
81	SCFsR Prothrombin	LDH-H1 CK-MB	0.906	0.858	1.764	0.92
82	PARC C1s	ERBB1 Prothrombin	0.878	0.878	1.756	0.914
83	HSP90a CDK5-p35	Kallikrein7 Contactin-5	0.873	0.884	1.757	0.92
84	HSP90a CK-MB	Prothrombin FYN	0.887	0.875	1.762	0.925
85	Prothrombin MEK1	CD30Ligand RAC1	0.901	0.849	1.751	0.914
86	SCFsR Prothrombin	C9 FGF-17	0.911	0.841	1.752	0.906
87	HSP90a CD30Ligand	Kallikrein7 TCTP	0.883	0.861	1.743	0.915
88	LRIG3 C1s	SCFsR AMPM2	0.892	0.864	1.756	0.916
89	Kallikrein7 HSP90a	Prothrombin BLC	0.887	0.852	1.74	0.908
90	PARC IGFBP-2	LRIG3 Ubiquitin + 1	0.883	0.872	1.755	0.922
91	RAC1 Contactin-5	PARC Ubiquitin + 1	0.887	0.869	1.757	0.925
92	RAC1 CNDP1	CD30Ligand Endostatin	0.883	0.875	1.758	0.916
93	IGFBP-2 C9	Prothrombin sL-Selectin	0.892	0.878	1.77	0.924
94	PTN IL-15Ra	UBE2N BTK	0.901	0.849	1.751	0.909
95	SCFsR BTK	Renin MEK1	0.901	0.849	1.751	0.9
96	CD30Ligand MIP-5	Kallikrein7 HSP90a	0.887	0.864	1.751	0.923

TABLE 25-continued

97	LRIG3	PARC	0.887	0.855	1.742	0.912
	C1s	TCTP				
98	CD30Ligand	LRIG3	0.892	0.864	1.756	0.919
	PARC	FYN				
99	PARC	LRIG3	0.85	0.889	1.739	0.923
	FYN	BLC				
100	SCFsR	CK-MB	0.883	0.872	1.755	0.923
	CSK	Kallikrein7				

Marker	Count	Marker	Count
PTN	100	CDK5-p35	19
Kallikrein7	100	ERBB1	14
SCFsR	99	FYN	13
IGFBP-2	88	Ubiquitin + 1	12
CD30Ligand	79	BMP-1	12
LRIG3	66	UBE2N	11
PARC	61	CyclophilinA	11
C9	61	CSK	11
C1s	55	CNDP1	11
Prothrombin	53	BLC	11
RAC1	50	AMPM2	11
sL-Selectin	42	TCTP	10
HSP90a	41	Midkine	10
Renin	38	MIP-5	10
BTK	38	MEK1	10
GAPDH, liver	31	IL-15Ra	10
KPCI	30	FGF-17	10
CK-MB	27	Endostatin	10
LDH-H1	25	Contactin-5	10

TABLE 26

100 Panels of 14 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers				
1	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	Midkine	CK-MB	PARC	C1s
2	PTN	RAC1	IGFBP-2	PARC	SCFsR
	CyclophilinA	Renin	C1s	Prothrombin	LDH-H1
3	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
	C1s	RAC1	Renin	HSP90a	BMP-1
4	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	C9	C1s	FYN	sL-Selectin
5	CD30Ligand	SCFsR	RAC1	C9	PTN
	Kallikrein7	CNDP1	BTK	sL-Selectin	Endostatin
6	PTN	C9	CSK	CD30Ligand	SCFsR
	LRIG3	IGFBP-2	Renin	CDK5-p35	C1s
7	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	C9	Kallikrein7	LRIG3	sL-Selectin	Ubiquitin + 1
8	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	C9	BTK	sL-Selectin	ERBB1	FYN
9	PTN	RAC1	IGFBP-2	PARC	SCFsR
	FGF-17	Kallikrein7	LRIG3	C9	C1s
10	C1s	SCFsR	GAPDH, liver	C9	PTN
	Kallikrein7	UBE2N	LRIG3	sL-Selectin	CNDP1
11	CD30Ligand	SCFsR	RAC1	C9	PTN
	Kallikrein7	Prothrombin	LRIG3	PARC	FGF-17
12	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	Kallikrein7	LDH-H1	CDK5-p35	Prothrombin	MIP-5
13	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
	SCFsR	BMP-1	Renin	RAC1	CD30Ligand
14	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	C9	BTK	sL-Selectin	Renin	PARC
15	PTN	RAC1	IGFBP-2	PARC	SCFsR
	sL-Selectin	C1s	LDH-H1	Prothrombin	Kallikrein7
16	IGFBP-2	KPCI	CD30Ligand	SCFsR	Kallikrein7
	Renin	CK-MB	C1s	Prothrombin	PARC
17	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
	PARC	CDK5-p35	Kallikrein7	sL-Selectin	LDH-H1
18	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	C9	C1s	Prothrombin	Endostatin
19	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand
	Kallikrein7	PARC	C1s	C9	Ubiquitin + 1
20	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
	LRIG3	CK-MB	PARC	Renin	C1s

TABLE 26-continued

21	PARC	SCFsR	HSP90a	PTN	IGFBP-2
	RAC1	CD30Ligand	Kallikrein7	CK-MB	C9
22	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
	C9	LDH-H1	CD30Ligand	Prothrombin	KPCI
23	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	Midkine	CK-MB	PARC	C1s
24	PTN	RAC1	IGFBP-2	PARC	SCFsR
	sL-Selectin	C1s	Kallikrein7	Prothrombin	C9
25	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	C9	C1s	FGF-17	BTK
26	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
	CDK5-p35	CSK	LRIG3	Renin	Ubiquitin + 1
27	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2
	PARC	C1s	CK-MB	LDH-H1	FGF-17
28	CD30Ligand	CyclophilinA	C9	SCFsR	PTN
	Prothrombin	GAPDH, liver	LRIG3	sL-Selectin	CNDP1
29	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	C9	Kallikrein7	LRIG3	Prothrombin	HSP90a
30	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
	LRIG3	CK-MB	PARC	Renin	C1s
31	CD30Ligand	CyclophilinA	C9	SCFsR	PTN
	Prothrombin	GAPDH, liver	LRIG3	sL-Selectin	CNDP1
32	CD30Ligand	SCFsR	RAC1	C9	PTN
	Kallikrein7	CNDP1	LRIG3	sL-Selectin	IGFBP-2
33	Kallikrein7	SCFsR	HSP90a	PTN	ERBB1
	CK-MB	PARC	LDH-H1	LRIG3	C1s
34	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	C9	BTK	sL-Selectin	KPCI	Prothrombin
35	C1s	SCFsR	GAPDH, liver	C9	PTN
	Kallikrein7	UBE2N	IGFBP-2	PARC	FYN
36	PTN	RAC1	IGFBP-2	PARC	SCFsR
	CyclophilinA	sL-Selectin	BMP-1	C1s	Midkine
37	PTN	C9	CSK	CD30Ligand	SCFsR
	LRIG3	IGFBP-2	Renin	Prothrombin	C1s
38	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	C9	BTK	sL-Selectin	ERBB1	FYN
39	CD30Ligand	SCFsR	KPCI	C9	BTK
	C1s	IGFBP-2	sL-Selectin	RAC1	CDK5-p35
40	PTN	SCFsR	RAC1	HSP90a	LRIG3
	IGFBP-2	Prothrombin	Kallikrein7	Renin	BTK
41	CD30Ligand	SCFsR	RAC1	C9	PTN
	IGFBP-2	LDH-H1	BTK	Renin	Prothrombin
42	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR
	RAC1	PARC	sL-Selectin	C9	MIP-5
43	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
	SCFsR	BMP-1	Renin	RAC1	CD30Ligand
44	CD30Ligand	SCFsR	RAC1	C9	PTN
	IGFBP-2	LDH-H1	BTK	Renin	Prothrombin
45	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	C9	BTK	sL-Selectin	PARC	C1s
46	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	C9	BTK	sL-Selectin	PARC	C1s
47	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin
	LDH-H1	PARC	Renin	C1s	CSK
48	Kallikrein7	SCFsR	HSP90a	PTN	KPCI
	Renin	CDK5-p35	BTK	BMP-1	Prothrombin
49	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	C9	Kallikrein7	LRIG3	sL-Selectin	HSP90a
50	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	Kallikrein7	LDH-H1	Prothrombin	Renin	LRIG3
51	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	Kallikrein7	LDH-H1	Prothrombin	Renin	LRIG3
52	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
	C9	LDH-H1	CD30Ligand	Prothrombin	KPCI
53	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	C9	C1s	Prothrombin	CD30Ligand
54	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	C9	Kallikrein7	LRIG3	sL-Selectin	Ubiquitin + 1
55	PTN	RAC1	IGFBP-2	PARC	SCFsR
	FYN	CD30Ligand	GAPDH, liver	C1s	Prothrombin
56	IGFBP-2	KPCI	CD30Ligand	SCFsR	Kallikrein7
	Renin	CK-MB	C1s	Prothrombin	PARC
57	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	C9	UBE2N	RAC1	CD30Ligand	sL-Selectin
58	CD30Ligand	SCFsR	RAC1	C9	PTN
	Kallikrein7	CNDP1	LRIG3	sL-Selectin	IGFBP-2
59	CD30Ligand	C9	GAPDH, liver	SCFsR	PTN
	sL-Selectin	Kallikrein7	IGFBP-2	PARC	LRIG3
60	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	C1s	Prothrombin	sL-Selectin	C9

TABLE 26-continued

61	CD30Ligand	SCFsR	RAC1	C9	PTN
	Kallikrein7	Prothrombin	MIP-5	CNDP1	UBE2N
62	CD30Ligand	KPCI	PTN	SCFsR	HSP90a
	IGFBP-2	CK-MB	Renin	Kallikrein7	C1s
63	PTN	RAC1	IGFBP-2	PARC	SCFsR
	CD30Ligand	GAPDH, liver	Renin	BTK	C9
64	PTN	RAC1	IGFBP-2	PARC	SCFsR
	CyclophilinA	Renin	C1s	CK-MB	Midkine
65	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	BMP-1	Renin	CD30Ligand	CyclophilinA
66	PTN	C9	CSK	CD30Ligand	SCFsR
	LRIG3	IGFBP-2	Renin	CDK5-p35	Prothrombin
67	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR
	PARC	Renin	CD30Ligand	BMP-1	Prothrombin
68	PTN	RAC1	IGFBP-2	PARC	SCFsR
	sL-Selectin	C1s	Kallikrein7	Prothrombin	C9
69	PTN	RAC1	IGFBP-2	PARC	sL-Selectin
	Prothrombin	SCFsR	C1s	LRIG3	GAPDH, liver
70	PTN	RAC1	IGFBP-2	PARC	SCFsR
	CD30Ligand	GAPDH, liver	Renin	BTK	Prothrombin
71	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
	C9	LDH-H1	CD30Ligand	Prothrombin	KPCI
72	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	C9	BTK	sL-Selectin	CNDP1	C1s
73	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR
	Renin	CK-MB	C1s	Ubiquitin + 1	PARC
74	IGFBP-2	SCFsR	KPCI	PTN	C1s
	CD30Ligand	C9	CSK	PARC	LRIG3
75	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
	C1s	RAC1	Renin	HSP90a	BMP-1
76	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Renin	Kallikrein7	BTK	CNDP1	Ubiquitin + 1
77	CD30Ligand	SCFsR	RAC1	C9	PTN
	Kallikrein7	Prothrombin	MIP-5	CNDP1	UBE2N
78	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	BMP-1	Renin	CD30Ligand	KPCI
79	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	C9	BTK	sL-Selectin	PARC	C1s
80	PTN	RAC1	IGFBP-2	PARC	SCFsR
	sL-Selectin	C1s	LDH-H1	Prothrombin	Kallikrein7
81	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
	CDK5-p35	CSK	Prothrombin	Renin	C1s
82	CD30Ligand	C9	GAPDH, liver	SCFsR	PTN
	sL-Selectin	Kallikrein7	IGFBP-2	RAC1	PARC
83	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3
	PARC	FYN	C1s	RAC1	C9
84	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3
	PARC	BTK	CDK5-p35	C1s	C9
85	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand
	PARC	Kallikrein7	CK-MB	C1s	Ubiquitin + 1
86	CD30Ligand	SCFsR	RAC1	C9	PTN
	Kallikrein7	Prothrombin	MIP-5	ERBB1	CyclophilinA
87	IGFBP-2	SCFsR	KPCI	PTN	C1s
	CD30Ligand	Renin	Ubiquitin + 1	LRIG3	HSP90a
88	SCFsR	C9	UBE2N	C1s	PTN
	IGFBP-2	Kallikrein7	PARC	Prothrombin	CDK5-p35
89	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	C9	BTK	sL-Selectin	PARC	CDK5-p35
90	CD30Ligand	C9	GAPDH, liver	SCFsR	PTN
	sL-Selectin	Kallikrein7	UBE2N	Endostatin	CNDP1
91	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
	CDK5-p35	CSK	Prothrombin	Renin	C1s
92	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	C9	BTK	sL-Selectin	ERBB1	GAPDH, liver
93	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	BMP-1	Renin	Prothrombin	IL-15Ra
94	PTN	RAC1	IGFBP-2	PARC	SCFsR
	LRIG3	C1s	Prothrombin	sL-Selectin	C9
95	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin
	LDH-H1	PARC	Renin	FYN	BMP-1
96	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
	SCFsR	BMP-1	Renin	RAC1	CD30Ligand
97	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	C9	BTK	LDH-H1	Prothrombin	CK-MB
98	BTK	RAC1	ERBB1	Kallikrein7	IGFBP-2
	PARC	C1s	BMP-1	sL-Selectin	CD30Ligand
99	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
	CDK5-p35	CSK	Prothrombin	Renin	C1s

TABLE 26-continued

100	PTN RAC1	GAPDH, liver PARC	IGFBP-2 sL-Selectin	LRIG3 C9	SCFsR BTK	
	Biomarkers		Sensitivity	Specificity	Sens. + Spec.	AUC
1	CD30Ligand sL-Selectin	Renin FYN	0.887	0.875	1.762	0.921
2	Kallikrein7 CK-MB	CD30Ligand BLC	0.878	0.872	1.75	0.927
3	SCFsR FYN	CDK5-p35 Prothrombin	0.915	0.849	1.765	0.909
4	HSP90a CDK5-p35	Kallikrein7 Prothrombin	0.897	0.881	1.777	0.923
5	C1s Prothrombin	GAPDH, liver LRIG3	0.901	0.866	1.768	0.921
6	GAPDH, liver Prothrombin	Kallikrein7 RAC1	0.897	0.866	1.763	0.919
7	RAC1 FYN	PARC Contactin-5	0.901	0.864	1.765	0.924
8	LRIG3 GAPDH, liver	SCFsR C1s	0.887	0.886	1.774	0.925
9	HSP90a CDK5-p35	Prothrombin FYN	0.897	0.869	1.766	0.919
10	Prothrombin RAC1	CD30Ligand IL-15Ra	0.906	0.858	1.764	0.918
11	C1s BTK	GAPDH, liver MEK1	0.892	0.866	1.758	0.908
12	RAC1 LRIG3	CD30Ligand CK-MB	0.901	0.861	1.762	0.921
13	Prothrombin TCTP	C1s FGF-17	0.906	0.847	1.753	0.905
14	CD30Ligand CyclophilinA	LRIG3 BMP-1	0.892	0.869	1.761	0.919
15	CD30Ligand BLC	GAPDH, liver FYN	0.887	0.861	1.748	0.922
16	CSK LDH-H1	PTN Midkine	0.906	0.855	1.761	0.915
17	BTK GAPDH, liver	ERBB1 Contactin-5	0.897	0.866	1.763	0.922
18	HSP90a CDK5-p35	Kallikrein7 FYN	0.897	0.872	1.769	0.922
19	BTK Prothrombin	sL-Selectin IL-15Ra	0.887	0.875	1.762	0.924
20	Kallikrein7 UBE2N	LDH-H1 MEK1	0.873	0.884	1.757	0.92
21	Prothrombin CyclophilinA	LRIG3 MIP-5	0.897	0.864	1.76	0.923
22	TCTP IGFBP-2	PTN CDK5-p35	0.897	0.855	1.752	0.908
23	CD30Ligand LRIG3	Renin Prothrombin	0.892	0.869	1.761	0.922
24	CD30Ligand CDK5-p35	GAPDH, liver BLC	0.864	0.884	1.747	0.928
25	HSP90a CNDP1	Kallikrein7 Prothrombin	0.887	0.878	1.765	0.918
26	SCFsR PARC	C9 C1s	0.892	0.866	1.758	0.914
27	PTN C9	SCFsR Contactin-5	0.869	0.892	1.761	0.928
28	Kallikrein7 RAC1	C1s Endostatin	0.906	0.858	1.764	0.919
29	RAC1 IL-15Ra	PARC FYN	0.906	0.855	1.761	0.919
30	Kallikrein7 CyclophilinA	LDH-H1 MEK1	0.869	0.886	1.755	0.92
31	Kallikrein7 RAC1	C1s MIP-5	0.901	0.858	1.759	0.918
32	C1s Prothrombin	GAPDH, liver TCTP	0.897	0.852	1.749	0.915
33	CyclophilinA UBE2N	IGFBP-2 C9	0.883	0.886	1.769	0.925
34	CD30Ligand CDK5-p35	LRIG3 Midkine	0.92	0.841	1.761	0.905
35	Prothrombin sL-Selectin	CD30Ligand BLC	0.864	0.884	1.747	0.924
36	Kallikrein7 Renin	CD30Ligand CK-MB	0.878	0.886	1.764	0.93
37	GAPDH, liver FGF-17	Kallikrein7 BTK	0.892	0.866	1.758	0.913

TABLE 26-continued

38	LRIG3 GAPDH, liver	SCFsR Contactin-5	0.883	0.878	1.76	0.923
39	PTN Endostatin	Kallikrein7 LRIG3	0.897	0.866	1.763	0.914
40	PARC FGF-17	C9 IL-15Ra	0.887	0.872	1.759	0.922
41	LRIG3 sL-Selectin	Kallikrein7 MEK1	0.897	0.858	1.755	0.911
42	CD30Ligand HSP90a	Kallikrein7 Prothrombin	0.892	0.866	1.758	0.923
43	Prothrombin TCTP	C1s PARC	0.901	0.847	1.748	0.907
44	LRIG3 PARC	Kallikrein7 Ubiquitin + 1	0.906	0.864	1.77	0.922
45	CD30Ligand FYN	LRIG3 CK-MB	0.887	0.872	1.759	0.923
46	CD30Ligand Endostatin	LRIG3 BLC	0.869	0.875	1.744	0.917
47	SCFsR Kallikrein7	CK-MB Midkine	0.892	0.866	1.758	0.922
48	CD30Ligand Contactin-5	IGFBP-2 PARC	0.897	0.864	1.76	0.913
49	RAC1 CDK5-p35	PARC IL-15Ra	0.901	0.858	1.759	0.924
50	RAC1 MEK1	CD30Ligand CNDP1	0.887	0.866	1.754	0.912
51	RAC1 CDK5-p35	CD30Ligand MIP-5	0.892	0.866	1.758	0.918
52	TCTP IGFBP-2	PTN FYN	0.901	0.847	1.748	0.904
53	HSP90a UBE2N	Kallikrein7 FGF-17	0.892	0.872	1.764	0.918
54	RAC1 FYN	PARC CD30Ligand	0.901	0.864	1.765	0.928
55	Kallikrein7 C9	sL-Selectin BLC	0.869	0.875	1.744	0.926
56	CSK AMPM2	PTN Midkine	0.906	0.852	1.758	0.911
57	LRIG3 Contactin-5	SCFsR CK-MB	0.873	0.886	1.76	0.928
58	C1s BTK	GAPDH, liver Endostatin	0.887	0.875	1.762	0.922
59	CyclophilinA RAC1	C1s IL-15Ra	0.892	0.866	1.758	0.926
60	HSP90a CK-MB	Kallikrein7 MEK1	0.873	0.878	1.751	0.92
61	C1s Endostatin	GAPDH, liver sL-Selectin	0.892	0.864	1.756	0.919
62	LRIG3 Prothrombin	PARC TCTP	0.887	0.858	1.745	0.913
63	Kallikrein7 LRIG3	FGF-17 Ubiquitin + 1	0.901	0.861	1.762	0.926
64	Kallikrein7 LDH-H1	CD30Ligand BLC	0.869	0.875	1.744	0.925
65	HSP90a CDK5-p35	Kallikrein7 Midkine	0.892	0.872	1.764	0.921
66	GAPDH, liver Ubiquitin + 1	Kallikrein7 C1s	0.883	0.875	1.758	0.921
67	KPCI Contactin-5	HSP90a Endostatin	0.887	0.872	1.759	0.912
68	CD30Ligand BTK	GAPDH, liver IL-15Ra	0.892	0.866	1.758	0.926
69	CD30Ligand C9	Kallikrein7 MEK1	0.873	0.878	1.751	0.92
70	Kallikrein7 LDH-H1	FGF-17 MIP-5	0.892	0.864	1.756	0.919
71	TCTP IGFBP-2	PTN Contactin-5	0.892	0.852	1.744	0.907
72	CD30Ligand CK-MB	LRIG3 Midkine	0.892	0.866	1.758	0.919
73	KPCI Prothrombin	CD30Ligand BLC	0.883	0.861	1.743	0.918
74	Kallikrein7 sL-Selectin	Prothrombin GAPDH, liver	0.897	0.861	1.758	0.913
75	SCFsR BTK	CDK5-p35 IL-15Ra	0.906	0.852	1.758	0.907
76	SCFsR C9	LDH-H1 MEK1	0.901	0.849	1.751	0.913
77	C1s Endostatin	GAPDH, liver BTK	0.911	0.844	1.755	0.916

TABLE 26-continued

78	HSP90a CDK5-p35	Kallikrein7 TCTP	0.892	0.852	1.744	0.91
79	CD30Ligand CK-MB	LRIG3 Prothrombin	0.892	0.866	1.758	0.924
80	CD30Ligand BLC	GAPDH, liver Midkine	0.873	0.869	1.743	0.923
81	SCFsR RAC1	C9 LRIG3	0.911	0.847	1.757	0.908
82	CyclophilinA Prothrombin	C1s Contactin-5	0.901	0.858	1.759	0.923
83	IGFBP-2 ERBB1	Prothrombin sL-Selectin	0.878	0.889	1.767	0.926
84	IGFBP-2 RAC1	Prothrombin IL-15Ra	0.897	0.861	1.758	0.919
85	BTK MEK1	Renin Midkine	0.878	0.872	1.75	0.92
86	C1s PARC	GAPDH, liver BTK	0.911	0.844	1.755	0.919
87	Kallikrein7 PARC	Prothrombin TCTP	0.897	0.847	1.743	0.906
88	RAC1 HSP90a	CD30Ligand sL-Selectin	0.897	0.866	1.763	0.924
89	CD30Ligand Renin	LRIG3 FYN	0.883	0.875	1.758	0.92
90	CyclophilinA LRIG3	C1s BLC	0.873	0.869	1.743	0.92
91	SCFsR UBE2N	C9 LRIG3	0.901	0.855	1.757	0.908
92	LRIG3 C1s	SCFsR Contactin-5	0.864	0.895	1.759	0.924
93	HSP90a CDK5-p35	Kallikrein7 BTK	0.887	0.869	1.757	0.921
94	HSP90a MEK1	Kallikrein7 FYN	0.878	0.872	1.75	0.913
95	SCFsR RAC1	CK-MB MIP-5	0.878	0.875	1.753	0.92
96	Prothrombin TCTP	C1s CDK5-p35	0.911	0.832	1.743	0.906
97	CD30Ligand CNDP1	LRIG3 RAC1	0.897	0.861	1.758	0.914
98	PTN UBE2N	SCFsR BLC	0.864	0.878	1.742	0.923
99	SCFsR CK-MB	C9 Midkine	0.901	0.855	1.757	0.917
100	CD30Ligand C1s	Kallikrein7 Contactin-5	0.878	0.881	1.759	0.927

Marker	Count	Marker	Count
SCFsR	100	KPCI	23
PTN	100	FYN	19
Kallikrein7	99	CyclophilinA	14
IGFBP-2	91	CNDP1	14
CD30Ligand	80	BMP-1	14
C1s	76	Midkine	13
PARC	69	UBE2N	12
LRIG3	68	ERBB1	12
Prothrombin	67	Ubiquitin + 1	11
C9	67	Contactin-5	11
RAC1	66	CSK	11
sL-Selectin	46	BLC	11
Renin	42	AMPM2	11
GAPDH, liver	41	TCTP	10
BTK	40	MIP-5	10
HSP90a	37	MEK1	10
CDK5-p35	27	IL-15Ra	10
CK-MB	25	FGF-17	10
LDH-H1	23	Endostatin	10

TABLE 27

100 Panels of 15 Asymptomatic Smokers vs. Cancer Biomarkers

	Biomarkers				
1	PTN BTK	SCFsR LDH-H1	AMPM2 Prothrombin	IGFBP-2 CK-MB	Kallikrein7 CNDP1

TABLE 27-continued

2	PTN	RAC1	IGFBP-2	PARC	SCFsR
	CD30Ligand	GAPDH, liver	C1s	Prothrombin	C9
3	CD30Ligand	CyclophilinA	C9	SCFsR	PTN
	GAPDH, liver	LRIG3	sL-Selectin	CNDP1	RAC1
4	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	C1s	CSK	PARC	CK-MB
5	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	BTK	sL-Selectin	ERBB1	GAPDH, liver	C1s
6	PTN	RAC1	IGFBP-2	PARC	SCFsR
	Renin	C1s	CK-MB	LDH-H1	BMP-1
7	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR
	PARC	sL-Selectin	C9	BTK	IL-15Ra
8	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
	BMP-1	Renin	RAC1	CD30Ligand	Endostatin
9	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
	CK-MB	PARC	Renin	C1s	UBE2N
10	C1s	SCFsR	GAPDH, liver	C9	PTN
	UBE2N	LRIG3	sL-Selectin	CNDP1	RAC1
11	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	C1s	SCFsR	CyclophilinA	ERBB1	C9
12	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
	LDH-H1	CD30Ligand	Prothrombin	KPCI	IGFBP-2
13	CD30Ligand	SCFsR	RAC1	C9	PTN
	CNDP1	BTK	sL-Selectin	Endostatin	LRIG3
14	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	LDH-H1	Prothrombin	CK-MB	CNDP1
15	PTN	RAC1	IGFBP-2	PARC	SCFsR
	Renin	CK-MB	Midkine	C1s	sL-Selectin
16	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	C1s	CSK	PARC	CK-MB
17	LRIG3	IGFBP-2	HSP90a	PARC	PTN
	ERBB1	LDH-H1	CK-MB	GAPDH, liver	C1s
18	C1s	SCFsR	GAPDH, liver	C9	PTN
	UBE2N	LRIG3	sL-Selectin	CNDP1	RAC1
19	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	PARC	CDK5-p35	C1s
20	PTN	LRIG3	CD30Ligand	GAPDH, liver	PARC
	IGFBP-2	RAC1	C9	Kallikrein7	FGF-17
21	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
	BMP-1	Renin	RAC1	PARC	CD30Ligand
22	PTN	RAC1	IGFBP-2	PARC	SCFsR
	Renin	C1s	CK-MB	Midkine	LDH-H1
23	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin
	PARC	Renin	C1s	CSK	Kallikrein7
24	IGFBP-2	SCFsR	KPCI	PTN	C1s
	Renin	RAC1	HSP90a	Contactin-5	BMP-1
25	PTN	LRIG3	CD30Ligand	GAPDH, liver	PARC
	IGFBP-2	RAC1	C9	Kallikrein7	FGF-17
26	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
	CK-MB	PARC	Renin	C1s	UBE2N
27	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	LDH-H1	Prothrombin	Renin	LRIG3	CDK5-p35
28	PTN	RAC1	IGFBP-2	PARC	SCFsR
	BMP-1	Renin	CD30Ligand	LDH-H1	CK-MB
29	CD30Ligand	CyclophilinA	C9	SCFsR	PTN
	GAPDH, liver	LRIG3	sL-Selectin	CNDP1	Ubiquitin + 1
30	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	PARC	CDK5-p35	C1s
31	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
	CK-MB	PARC	Renin	C1s	CyclophilinA
32	PTN	C9	CSK	CD30Ligand	SCFsR
	IGFBP-2	Renin	CDK5-p35	Prothrombin	Ubiquitin + 1
33	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	BTK	sL-Selectin	ERBB1	GAPDH, liver	C1s
34	PTN	LRIG3	CD30Ligand	GAPDH, liver	PARC
	IGFBP-2	RAC1	C9	Kallikrein7	C1s
35	IGFBP-2	KPCI	CD30Ligand	SCFsR	LRIG3
	C9	BTK	Renin	CDK5-p35	RAC1
36	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR
	PARC	sL-Selectin	C9	BTK	Renin
37	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	BTK	CNDP1	Ubiquitin + 1	C9
38	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	PARC	C1s	CK-MB
39	PTN	RAC1	IGFBP-2	PARC	SCFsR
	Renin	LDH-H1	C1s	Midkine	CDK5-p35
40	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin
	PARC	Renin	C1s	CSK	Kallikrein7
41	PTN	RAC1	IGFBP-2	PARC	SCFsR
	CD30Ligand	GAPDH, liver	C1s	Prothrombin	C9

TABLE 27-continued

42	PARC	SCFsR	HSP90a	PTN	IGFBP-2
	CD30Ligand	Kallikrein7	sL-Selectin	C9	C1s
43	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3
	CDK5-p35	PARC	Prothrombin	Renin	CyclophilinA
44	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	BTK	CNDP1	BMP-1	Prothrombin
45	CD30Ligand	CyclophilinA	C9	SCFsR	PTN
	GAPDH, liver	LRIG3	sL-Selectin	CNDP1	RAC1
46	KPCI	HSP90a	PTN	Kallikrein7	IGFBP-2
	BMP-1	Renin	RAC1	CD30Ligand	Midkine
47	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	PARC	C1s	CK-MB
48	PTN	C9	CSK	CD30Ligand	SCFsR
	IGFBP-2	Renin	CDK5-p35	Prothrombin	Ubiquitin + 1
49	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin
	PARC	Renin	C1s	GAPDH, liver	Kallikrein7
50	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	BTK	sL-Selectin	ERBB1	GAPDH, liver	C1s
51	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	Kallikrein7	LRIG3	Prothrombin	HSP90a	IL-15Ra
52	BTK	IGFBP-2	PTN	Kallikrein7	SCFsR
	Renin	CD30Ligand	BMP-1	Prothrombin	Contactin-5
53	PARC	SCFsR	HSP90a	PTN	IGFBP-2
	CD30Ligand	Kallikrein7	CK-MB	C9	CyclophilinA
54	CD30Ligand	SCFsR	RAC1	C9	PTN
	CNDP1	LRIG3	sL-Selectin	IGFBP-2	Prothrombin
55	IGFBP-2	SCFsR	GAPDH, liver	PTN	CD30Ligand
	Kallikrein7	CK-MB	C1s	Ubiquitin + 1	FGF-17
56	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	C1s	CSK	PARC	CK-MB
57	CyclophilinA	HSP90a	ERBB1	SCFsR	PARC
	C9	LRIG3	sL-Selectin	FYN	C1s
58	CD30Ligand	SCFsR	RAC1	C9	PTN
	CNDP1	BTK	sL-Selectin	Prothrombin	LRIG3
59	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	PARC	C1s	CK-MB
60	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	C1s	GAPDH, liver	PARC	CK-MB
61	PTN	RAC1	IGFBP-2	PARC	SCFsR
	GAPDH, liver	Renin	BTK	Prothrombin	LDH-H1
62	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
	LDH-H1	CD30Ligand	Prothrombin	KPCI	IGFBP-2
63	Kallikrein7	CyclophilinA	SCFsR	IGFBP-2	CD30Ligand
	LRIG3	CK-MB	PARC	HSP90a	C9
64	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
	CSK	Prothrombin	Renin	C1s	RAC1
65	C1s	SCFsR	GAPDH, liver	C9	PTN
	UBE2N	LRIG3	sL-Selectin	CNDP1	RAC1
66	PTN	LRIG3	CD30Ligand	GAPDH, liver	PARC
	IGFBP-2	RAC1	C9	Kallikrein7	FGF-17
67	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	BTK	CNDP1	C9	GAPDH, liver
68	IGFBP-2	KPCI	CD30Ligand	SCFsR	LRIG3
	C9	BTK	Renin	CDK5-p35	RAC1
69	CD30Ligand	KPCI	PTN	SCFsR	HSP90a
	CK-MB	Renin	Kallikrein7	C1s	Prothrombin
70	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	CNDP1	C1s	PARC
71	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
	C1s	CK-MB	PARC	BTK	Midkine
72	CD30Ligand	Kallikrein7	KPCI	PTN	IGFBP-2
	CSK	Prothrombin	Renin	C1s	Ubiquitin + 1
73	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3
	BTK	CDK5-p35	C1s	C9	RAC1
74	Kallikrein7	SCFsR	HSP90a	PTN	ERBB1
	PARC	LDH-H1	LRIG3	C1s	C9
75	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	BTK	CNDP1	Prothrombin	C1s
76	IGFBP-2	SCFsR	GAPDH, liver	PTN	C1s
	Kallikrein7	LRIG3	sL-Selectin	HSP90a	CDK5-p35
77	PTN	RAC1	IGFBP-2	PARC	SCFsR
	GAPDH, liver	Renin	BTK	C9	LRIG3
78	PTN	GAPDH, liver	IGFBP-2	LRIG3	SCFsR
	PARC	sL-Selectin	C9	BTK	Midkine
79	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
	LDH-H1	CD30Ligand	Prothrombin	KPCI	IGFBP-2
80	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	PARC	CDK5-p35	C1s
81	Kallikrein7	LRIG3	HSP90a	PTN	IGFBP-2
	PARC	Renin	CD30Ligand	LDH-H1	BMP-1

TABLE 27-continued

82	LRIG3	IGFBP-2	HSP90a	PTN	Prothrombin
	PARC	Renin	C1s	CSK	Kallikrein7
83	Kallikrein7	SCFsR	HSP90a	PTN	LRIG3
	FYN	C1s	RAC1	C9	CDK5-p35
84	CD30Ligand	SCFsR	RAC1	C9	PTN
	LDH-H1	BTK	Endostatin	CNDP1	sL-Selectin
85	PTN	RAC1	IGFBP-2	PARC	SCFsR
	C1s	Kallikrein7	Prothrombin	C9	BTK
86	CD30Ligand	IGFBP-2	PTN	RAC1	SCFsR
	CK-MB	PARC	Renin	C1s	CyclophilinA
87	CD30Ligand	SCFsR	RAC1	C9	PTN
	LDH-H1	BTK	Renin	Prothrombin	CK-MB
88	LRIG3	ERBB1	HSP90a	SCFsR	Kallikrein7
	LDH-H1	CD30Ligand	Prothrombin	KPCI	IGFBP-2
89	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	CNDP1	C1s	CK-MB
90	PTN	RAC1	IGFBP-2	PARC	SCFsR
	Renin	CK-MB	Midkine	C1s	Ubiquitin + 1
91	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	BTK	CNDP1	Prothrombin	C1s
92	PTN	RAC1	IGFBP-2	PARC	SCFsR
	Renin	C1s	sL-Selectin	GAPDH, liver	LDH-H1
93	CD30Ligand	SCFsR	RAC1	C9	PTN
	CNDP1	BTK	sL-Selectin	Endostatin	LRIG3
94	PTN	SCFsR	RAC1	HSP90a	LRIG3
	Prothrombin	Kallikrein7	Renin	BTK	FGF-17
95	PARC	Kallikrein7	HSP90a	PTN	IGFBP-2
	UBE2N	RAC1	C1s	sL-Selectin	Prothrombin
96	CD30Ligand	SCFsR	RAC1	C9	PTN
	Prothrombin	MIP-5	CNDP1	UBE2N	Endostatin
97	CD30Ligand	IGFBP-2	PTN	RAC1	LRIG3
	Kallikrein7	BTK	CNDP1	Prothrombin	C1s
98	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	Midkine	CK-MB	PARC	C1s	LRIG3
99	PTN	SCFsR	AMPM2	IGFBP-2	Kallikrein7
	BTK	sL-Selectin	PARC	C1s	FYN
100	CD30Ligand	KPCI	PTN	SCFsR	HSP90a
	CK-MB	Renin	Kallikrein7	C1s	Prothrombin

	Biomarkers			Sensitivity	Specificity	Sens. + Spec.	AUC
1	CD30Ligand	LRIG3	C9	0.906	0.858	1.764	0.916
	RAC1	C1s					
2	Kallikrein7	sL-Selectin	FYN	0.883	0.878	1.76	0.927
	CDK5-p35	BLC					
3	Kallikrein7	C1s	Prothrombin	0.911	0.861	1.772	0.919
	Endostatin	BMP-1					
4	SCFsR	LDH-H1	Renin	0.887	0.884	1.771	0.925
	BMP-1	Prothrombin					
5	LRIG3	SCFsR	C9	0.878	0.895	1.773	0.924
	Contactin-5	FYN					
6	Kallikrein7	CD30Ligand	BTK	0.878	0.892	1.77	0.927
	LRIG3	FGF-17					
7	CD30Ligand	Kallikrein7	RAC1	0.897	0.869	1.766	0.925
	Renin	Prothrombin					
8	Prothrombin	C1s	SCFsR	0.906	0.864	1.77	0.913
	CDK5-p35	PARC					
9	Kallikrein7	LDH-H1	LRIG3	0.883	0.884	1.766	0.92
	MEK1	BTK					
10	Prothrombin	CD30Ligand	Kallikrein7	0.901	0.861	1.762	0.921
	MIP-5	Endostatin					
11	LRIG3	sL-Selectin	Prothrombin	0.892	0.881	1.773	0.925
	GAPDH, liver	Midkine					
12	TCTP	PTN	C9	0.901	0.855	1.757	0.906
	CDK5-p35	FYN					
13	C1s	GAPDH, liver	Kallikrein7	0.915	0.858	1.773	0.921
	Ubiquitin + 1	Prothrombin					
14	CD30Ligand	LRIG3	C9	0.897	0.866	1.763	0.915
	UBE2N	C1s					
15	Kallikrein7	CD30Ligand	BTK	0.873	0.886	1.76	0.931
	GAPDH, liver	BLC					
16	SCFsR	LDH-H1	Renin	0.878	0.892	1.77	0.925
	BMP-1	FGF-17					
17	BTK	SCFsR	Kallikrein7	0.887	0.878	1.765	0.923
	Contactin-5	UBE2N					
18	Prothrombin	CD30Ligand	Kallikrein7	0.901	0.864	1.765	0.923
	IL-15Ra	PARC					
19	CD30Ligand	LRIG3	C9	0.887	0.875	1.762	0.912
	Prothrombin	MEK1					

TABLE 27-continued

20	HSP90a MIP-5	SCFsR Ubiquitin + 1	Prothrombin	0.906	0.855	1.761	0.918
21	Prothrombin CDK5-p35	C1s TCTP	SCFsR	0.906	0.849	1.756	0.909
22	Kallikrein7 Prothrombin	CD30Ligand BLC	CyclophilinA	0.878	0.875	1.753	0.927
23	SCFsR CD30Ligand	CK-MB GAPDH, liver	LDH-H1	0.892	0.869	1.761	0.922
24	Kallikrein7 Endostatin	Prothrombin BTK	CD30Ligand	0.901	0.864	1.765	0.908
25	HSP90a IL-15Ra	SCFsR FYN	Prothrombin	0.897	0.866	1.763	0.917
26	Kallikrein7 MEK1	LDH-H1 Prothrombin	LRIG3	0.878	0.884	1.761	0.921
27	RAC1 MIP-5	CD30Ligand Midkine	Kallikrein7	0.892	0.866	1.758	0.918
28	HSP90a Prothrombin	Kallikrein7 TCTP	LRIG3	0.892	0.861	1.753	0.921
29	Kallikrein7 BTK	C1s Endostatin	Prothrombin	0.915	0.852	1.768	0.919
30	CD30Ligand Midkine	LRIG3 CK-MB	C9	0.887	0.875	1.762	0.924
31	Kallikrein7 Midkine	LDH-H1 BLC	LRIG3	0.869	0.884	1.752	0.925
32	GAPDH, liver C1s	Kallikrein7 sL-Selectin	LRIG3	0.892	0.869	1.761	0.922
33	LRIG3 Contactin-5	SCFsR Prothrombin	C9	0.878	0.886	1.764	0.925
34	HSP90a IL-15Ra	SCFsR CDK5-p35	Prothrombin	0.897	0.866	1.763	0.921
35	PTN C1s	Prothrombin MEK1	Kallikrein7	0.906	0.855	1.761	0.905
36	CD30Ligand Prothrombin	Kallikrein7 MIP-5	RAC1	0.883	0.875	1.758	0.926
37	SCFsR sL-Selectin	LDH-H1 TCTP	Renin	0.906	0.847	1.753	0.914
38	CD30Ligand Midkine	LRIG3 FYN	C9	0.892	0.869	1.761	0.922
39	Kallikrein7 CK-MB	CD30Ligand BLC	CyclophilinA	0.883	0.869	1.752	0.927
40	SCFsR CD30Ligand	CK-MB AMPM2	LDH-H1	0.901	0.858	1.759	0.916
41	Kallikrein7 Contactin-5	sL-Selectin Midkine	FYN	0.892	0.872	1.764	0.926
42	Prothrombin UBE2N	LRIG3 FGF-17	RAC1	0.892	0.875	1.767	0.922
43	IGFBP-2 IL-15Ra	RAC1 FGF-17	C9	0.901	0.861	1.762	0.921
44	SCFsR GAPDH, liver	LDH-H1 MEK1	Renin	0.897	0.864	1.76	0.912
45	Kallikrein7 MIP-5	C1s CDK5-p35	Prothrombin	0.911	0.847	1.757	0.918
46	Prothrombin CDK5-p35	C1s TCTP	SCFsR	0.911	0.841	1.752	0.906
47	CD30Ligand Prothrombin	LRIG3 BLC	C9	0.873	0.878	1.751	0.923
48	GAPDH, liver C1s	Kallikrein7 PARC	LRIG3	0.878	0.881	1.759	0.925
49	SCFsR BTK	CK-MB Contactin-5	LDH-H1	0.892	0.872	1.764	0.926
50	LRIG3 CNDP1	SCFsR RAC1	C9	0.897	0.872	1.769	0.925
51	RAC1 sL-Selectin	PARC CDK5-p35	C9	0.906	0.855	1.761	0.924
52	KPCI RAC1	HSP90a MEK1	PARC	0.901	0.858	1.759	0.905
53	Prothrombin FGF-17	LRIG3 MIP-5	RAC1	0.887	0.869	1.757	0.923
54	C1s Ubiquitin + 1	GAPDH, liver TCTP	Kallikrein7	0.906	0.844	1.75	0.914
55	BTK Prothrombin	Renin BLC	PARC	0.854	0.895	1.749	0.929
56	SCFsR C9	LDH-H1 CDK5-p35	Renin	0.883	0.875	1.758	0.928
57	IGFBP-2 GAPDH, liver	Kallikrein7 CNDP1	PTN	0.897	0.872	1.769	0.923
58	C1s UBE2N	GAPDH, liver Endostatin	Kallikrein7	0.92	0.858	1.778	0.919
59	CD30Ligand Prothrombin	LRIG3 IL-15Ra	C9	0.883	0.878	1.76	0.922

TABLE 27-continued

60	SCFsR BTK	LDH-H1 MEK1	Renin	0.883	0.875	1.758	0.921
61	Kallikrein7 MIP-5	FGF-17 LRIG3	CD30Ligand	0.887	0.869	1.757	0.919
62	TCTP CDK5-p35	PTN PARC	C9	0.883	0.864	1.746	0.911
63	PTN FYN	Renin BLC	LDH-H1	0.873	0.875	1.748	0.922
64	SCFsR LRIG3	C9 PARC	CDK5-p35	0.897	0.861	1.758	0.912
65	Prothrombin Endostatin	CD30Ligand Contactin-5	Kallikrein7	0.887	0.875	1.762	0.919
66	HSP90a IL-15Ra	SCFsR BTK	Prothrombin	0.897	0.864	1.76	0.917
67	SCFsR C1s	LDH-H1 MEK1	Renin	0.892	0.864	1.756	0.914
68	PTN MIP-5	Prothrombin FYN	Kallikrein7	0.915	0.841	1.756	0.908
69	LRIG3 RAC1	PARC TCTP	IGFBP-2	0.897	0.849	1.746	0.911
70	CD30Ligand CK-MB	LRIG3 RAC1	C9	0.883	0.878	1.76	0.925
71	Kallikrein7 Prothrombin	KPCI BLC	Renin	0.887	0.861	1.748	0.919
72	SCFsR FGF-17	C9 LRIG3	CDK5-p35	0.901	0.855	1.757	0.91
73	IGFBP-2 Contactin-5	Prothrombin CNDP1	PARC	0.883	0.878	1.76	0.919
74	CyclophilinA FYN	IGFBP-2 UBE2N	CK-MB	0.883	0.884	1.766	0.924
75	SCFsR GAPDH, liver	LDH-H1 Endostatin	Renin	0.906	0.866	1.773	0.918
76	RAC1 IL-15Ra	PARC BTK	C9	0.911	0.849	1.76	0.923
77	Kallikrein7 Ubiquitin + 1	FGF-17 MEK1	CD30Ligand	0.892	0.864	1.756	0.919
78	CD30Ligand Renin	Kallikrein7 MIP-5	RAC1	0.878	0.878	1.756	0.927
79	TCTP CDK5-p35	PTN BTK	C9	0.901	0.844	1.745	0.905
80	CD30Ligand LDH-H1	LRIG3 Prothrombin	C9	0.897	0.864	1.76	0.919
81	CK-MB Prothrombin	SCFsR BLC	UBE2N	0.864	0.884	1.747	0.923
82	SCFsR CDK5-p35	CK-MB BMP-1	LDH-H1	0.878	0.878	1.756	0.923
83	IGFBP-2 Contactin-5	Prothrombin CD30Ligand	PARC	0.873	0.886	1.76	0.919
84	LRIG3 UBE2N	Kallikrein7 FGF-17	IGFBP-2	0.892	0.875	1.767	0.917
85	CD30Ligand IL-15Ra	GAPDH, liver CDK5-p35	sL-Selectin	0.887	0.872	1.759	0.926
86	Kallikrein7 MEK1	LDH-H1 Prothrombin	LRIG3	0.883	0.872	1.755	0.921
87	LRIG3 FGF-17	Kallikrein7 MIP-5	IGFBP-2	0.892	0.864	1.756	0.923
88	TCTP CDK5-p35	PTN Midkine	C9	0.892	0.852	1.744	0.908
89	CD30Ligand CyclophilinA	LRIG3 Midkine	C9	0.897	0.864	1.76	0.918
90	Kallikrein7 LDH-H1	CD30Ligand BLC	BTK	0.878	0.869	1.747	0.925
91	SCFsR CK-MB	LDH-H1 CSK	Renin	0.892	0.864	1.756	0.918
92	Kallikrein7 Contactin-5	CD30Ligand CDK5-p35	BTK	0.887	0.872	1.759	0.926
93	C1s Ubiquitin + 1	GAPDH, liver PARC	Kallikrein7	0.897	0.869	1.766	0.926
94	PARC IL-15Ra	C9 FYN	IGFBP-2	0.892	0.866	1.758	0.92
95	LRIG3 MEK1	SCFsR CDK5-p35	C9	0.897	0.858	1.755	0.915
96	C1s BTK	GAPDH, liver FGF-17	Kallikrein7	0.906	0.849	1.756	0.916
97	SCFsR CK-MB	LDH-H1 TCTP	Renin	0.892	0.852	1.744	0.919
98	CD30Ligand Prothrombin	Renin FYN	BTK	0.897	0.864	1.76	0.921
99	CD30Ligand CK-MB	LRIG3 BLC	C9	0.869	0.878	1.746	0.922

TABLE 27-continued

100	LRIG3 RAC1	PARC CSK	IGFBP-2	0.897	0.858	1.755	0.912

Marker	Count	Marker	Count
SCFsR	100	CNDP1	25
PTN	100	Midkine	16
Kallikrein7	100	KPCI	16
IGFBP-2	90	FGF-17	16
CD30Ligand	85	UBE2N	14
LRIG3	84	FYN	14
C1s	76	CyclophilinA	14
Prothrombin	72	BMP-1	13
PARC	70	AMPM2	13
RAC1	69	Ubiquitin + 1	12
C9	64	Endostatin	12
BTK	53	CSK	12
Renin	52	BLC	12
GAPDH, liver	43	TCTP	11
CK-MB	40	MIP-5	11
sL-Selectin	39	MEK1	11
LDH-H1	39	IL-15Ra	11
HSP90a	38	ERBB1	11
CDK5-p35	31	Contactin-5	11

TABLE 28

Aptamer Concentrations

Target	Final Aptamer Conc (nM)
AMPM2	0.5
Apo A-I	0.25
b-ECGF	2
BLC	0.25
BMP-1	1
BTK	0.25
C1s	0.25
C9	1
Cadherin E	0.25
Cadherin-6	0.5
Calpain I	0.5
Catalase	0.5
CATC	0.5
Cathepsin H	0.5
CD30 Ligand	0.5
CDK5/p35	0.5
CK-MB	1
CNDP1	0.5
Contactin-5	1
CSK	
Cyclophilin A	0.5
Endostatin	1
ERBB1	0.5
FYN	0.25
GAPDH, liver	0.25
HMG-1	0.5
HSP 90a	0.5
HSP 90b	0.5
IGFBP-2	1
IL-15 Ra	0.5
IL-17B	0.5
IMB1	1
Kallikrein 7	0.5
KPCI	0.25
LDH-H 1	0.5
LGMN	0.5
LRIG3	0.25
Macrophage mannose receptor	2
MEK1	0.5
METAP1	0.25
Midkine	0.5
MIP-5	1
MK13	1
MMP-7	0.25
NACA	0.5

TABLE 28-continued

Aptamer Concentrations

Target	Final Aptamer Conc (nM)
NAGK	0.5
PARC	0.5
Proteinase-3	1
Prothrombin	0.5
PTN	0.25
RAC1	0.5
Renin	0.25
RGM-C	0.5
SCF sR	1
sL-Selectin	0.5
TCTP	0.5
UBE2N	0.5
Ubiquitin + 1	0.5
VEGF	1
YES	0.5

TABLE 29

Site	NSCLC	Benign Nodule	Asymptomatic Smokers
1	32	0	47
2	63	176	128
3	70	195	94
4	54	49	83
Sum	213	420	352
Males	51%	46%	49%
Females	49%	54%	51%
Median Age	68	60	57
Median Pack Years	40	42	34
Median FEV1	1.94	2.43	2.58
Median FEV 1%	74	88	90
Median FEV1/FVC	70	72	73

TABLE 30

Biomarkers Identified in Benign Nodule-NSCLC in Aggregated Data

SCF sR	CNDP1	Stress-induced-phosphoprotein 1
RGM-C	MEK1	LRIG3
ERBB1	MDHC	ERK-1
Cadherin E	Catalase	Cyclophilin A
CK-MB	BMP-1	Caspase-3
METAP1	ART	UFM1
HSP90a	C9	RAC1
IGFBP-2	TCPTP	Peroxiredoxin-1
Calpain I	RPS6KA3	PAFAHbeta subunit
KPCI	IMB1	MK01
MMP-7	UBC9	Integrina1b1
β-ECGF	Ubiquitin + 1	IDE
HSP90b	Cathepsin H	CAMK2A
NAGK	CSK21	BLC
FGF-17	BTK	BARK1
Macrophage mannose receptor	Thrombin	eIF-5
MK13	LYN	UFC1
NACA	HSP70	RS7
GAPDH	UBE2N	PRKACA
CSK	TCTP	AMPM2
Activin A	RabGDPdissociation inhibitor beta	Stress-induced-phosphoprotein 1
Prothrombin	MAPKAPK3	

TABLE 31

Biomarkers Identified in Smoker-NSCLC in Aggregated Data

SCF sR	Renin	Caspase-3
PTN	CSK	AMPM2
HSP90a	Contactin-5	RS7
Kallikrein 7	UBE2N	OCAD1
LRIG3	MPIF-1	HSP70
IGFBP-2	PRKACA	GSK-3alpha
PARC	granzymeA	FSTL3
CD30 Ligand	Ubiquitin + 1	PAFAH beta subunit
Prothrombin	NAGK	Integrin a1b1
ERBB1	Cathepsin S	ERK-1
KPCI	TCTP	CSK21
BTK	UBC9	CATC
GAPDH, liver	MK13	MK01
CK-MB	Cystatin C	pTEN
LDH-H1	RPS6KA3	b2-Microglobulin
CNDP1	IL-15Ra	UFM1
RAC1	Calpain I	UFC1
C9	MAPKAPK3	Peroxiredoxin-1
FGF-17	IMB1	PKB
Endostatin	BARK1	IDE
Cyclophilin A	Cathepsin H	HSP90b
C1s	Macrophage mannose receptor	BGH3
CD30	Dtk	BLC
BMP-1	NACA	XPNPEP1
SBDS	RabGDPdissociation inhibitor beta	TNFsR-I
MIP-5	LYN	DUS3
CCL28	METAP1	
MMP-7	MK12	

TABLE 32

Biomarkers Identified in Benign Nodule-NSCLC by Site

ERBB1	FGF-17
LRIG3	CD30Ligand
HMG-1	LGMN
YES	Proteinase-3
C9	MEK1
MK13	BLC
Macrophage mannose receptor	IL-17B
ApoA-I	CATC

TABLE 32-continued

Biomarkers Identified in Benign Nodule-NSCLC by Site

CNDP1	Cadherin-6
BMP-1	

TABLE 33

Biomarkers Identified in Smoker-NSCLC by Site

Kallikrein 7	CSK	Azurocidin
SCF sR	FYN	b2-Microglobulin
ERBB1	BLC	OCAD1
C9	TCTP	LGMN
LRIG3	Midkine	PKB
AMPM2	FGF-17	XPNPEP1
HSP90a	MEK1	Cadherin-6
sL-Selectin	BMP-1	pTEN
BTK	LYN	LYNB
CNDP1	Integrin a1b1	DUS3
CDK5-p35	PKB gamma	Carbonic anhydrase XIII

TABLE 34

Biomarkers Identified in Benign Nodule-NSCLC in Blended Data Set

YES	Catalase	PAFAH beta subunit	eIF-5
MK13	Prothrombin	AMPM2	TNFsR-I
LRIG3	BTK	TCPTP	BLC
HMG-1	DRG-1	BGH3	MAPKAPK3
ERBB1	UBE2N	Ubiquitin + 1	b2-Microglobulin
Cadherin E	Activin A	BARK1	SOD
CK-MB	TCTP	LYN	GSK-3 alpha
C9	UBC9	PRKACA	Fibrinogen
SCFsR	NAGK	LGMN	ERK-1
CNDP1	Calpain I	Integrin a1b1	Cadherin-6
RGM-C	GAPDH	HSP70	IDE
METAP1	UFM1	XPNPEP1	UFC1
Macrophage mannose receptor	Caspase-3	Stress-induced-phosphoprotein1	PSA-ACT
BMP-1	b-ECGF	RPS6KA3	CATC
KPCI	RAC1	SHP-2	pTEN
IGFBP-2	MDHC	CEA	PSA
CSK	Proteinase-3	OCAD1	CATE
NACA	MK01	Cyclophilin A	Peroxiredoxin-1
IMB1	MEK1	RabGDP dissociation inhibitor beta	SBDS
Cathepsin H	HSP90a	DUS3	RS7
MMP-7	Thrombin	CAMK2A	Carbonic anhydrase XIII
VEGF	FGF-17	CaMKKalpha	
HSP90b	ART	CSK21	

TABLE 35

Biomarkers Identified in Smoker-NSCLC in Blended Data Set

SCFsR	UBE2N	CystatinC	GSK-3alpha
LRIG3	MIP-5	LYN	CATC
HSP90a	Contactin-5	MPIF-1	SBDS
ERBB1	Ubiquitin + 1	GCP-2	PAFAH beta subunit
C9	Macrophage mannose receptor	KPCI	IMB1
AMPM2	PRKACA	MK12	CSK21
Kallikrein 7	Cathepsin S	MAPKAPK3	PKB
PTN	BMP-1	Integrin a1b1	Dtk
PARC	Cyclophilin A	HSP70	DUS3
CD30 Ligand	CCL28	RPS6KA3	Calpain I
Prothrombin	Endostatin	NACA	TNFsR-I
CSK	Cathepsin H	RS7	PTP-1B
CK-MB	Granzyme A	Peroxiredoxin-1	IDE

TABLE 35-continued

Biomarkers Identified in Smoker-NSCLC in Blended Data Set			
BTK	GAPDH, liver	MMP-7	HSP90b
C1s	FGF-17	pTEN	Fibrinogen
IGFBP-2	BARK1	UFM1	Caspase-3
LDH-H1	BLC	UBC9	PSA-ACT
RAC1	RabGDP dissociation inhibitor beta	FSTL3	OCAD1
Renin	CD30	BGH3	SOD
CNDP1	MK13	UFC1	METAP1
TCTP	NAGK	MK01	PSA
IL-15Ra	b2-Microglobulin	ERK-1	

TABLE 36

Biomarkers for Lung Cancer	Benign Nodule	Smokers
AMPM2	YES	SCFsR
BMP-1	MK13	LRIG3
BTK	LRIG3	HSP90a
C1s	HMG-1	ERBB1
C9	ERBB1	C9
Cadherin E	CadherinE	AMPM2
Catalase	CK-MB	Kallikrein7
Cathepsin H	C9	PTN
CD30Ligand	SCFsR	PARC
CK-MB	CNDP1	CD30Ligand
CNDP1	RGM-C	Prothrombin
Contactin-5	METAP1	CSK
CSK	Macrophage mannose receptor	CK-MB
ERBB1	BMP-1	BTK
HMG-1	KPCI	C1s
HSP90a	IGFBP-2	IGFBP-2
HSP90b	CSK	LDH-H1
IGFBP-2	NACA	RAC1
IL-15Ra	IMB1	Renin
IMB1	CathepsinH	CNDP1
Kallikrein7	MMP-7	TCTP
KPCI	VEGF	IL-15Ra
LDH-H1	HSP90b	UBE2N
LRIG3	Catalase	MIP-5
Macrophage mannose receptor	Prothrombin	Contactin-5
METAP1	ApoA-I	Ubiquitin + 1
MIP-5	b-ECGF	BLC
MK13	BLC	BMP-1
MMP-7	Cadherin-6	CDK5-p35
NACA	Calpain I	CyclophilinA
PARC	CATC	Endostatin
Prothrombin	CD30Ligand	FGF-17
PTN	FGF-17	FYN
RAC1	GAPDH	GAPDH
Renin	HSP90a	KPCI
RGM-C	IL-17B	MEK1
SCF sR	LGMN	Midkine
TCTP	MEK1	sL-Selectin
UBE2N	NAGK	
Ubiquitin + 1	Proteinase-3	
VEGF		
YES		
ApoA-I		
b-ECGF		
BLC		
Cadherin-6		
Calpain I		
CATC		
CDK5-p35		
CyclophilinA		
Endostatin		
FYN		
FGF-17		
GAPDH		
IL-17B		
LGMN		
MEK1		
Midkine		
NAGK		

TABLE 36-continued

Biomarkers for Lung Cancer	Benign Nodule	Smokers
Proteinase-3		
sL-Selectin		

TABLE 37

Aptamer To Designated Biomarker	Solution K_d (M)	Assay LLOQ (M)	Up or Down Regulated
AMPM2	3×10^{-10}	NM	Up
Apo A-I	9×10^{-09}	2×10^{-11}	Down
β-ECGF	1×10^{-10} (pool)	NM	Up
BLC	5×10^{-10} (pool)	7×10^{-14}	Up
BMP-1	2×10^{-10}	9×10^{-13}	Down
BTK	8×10^{-10} (pool)	2×10^{-13}	Up
C1s	8×10^{-09}	7×10^{-12}	Up
C9	1×10^{-11}	1×10^{-14}	Down
Cadherin E	3×10^{-10}	2×10^{-12}	Down
Cadherin-6	2×10^{-09}	2×10^{-12}	Up
Calpain I	2×10^{-11}	7×10^{-14}	Up
Catalase	7×10^{-10} (pool)	8×10^{-14}	Up
CATC	8×10^{-08}	NM	Up
Cathepsin H	1×10^{-09} (pool)	8×10^{-13}	Up
CD30 Ligand	2×10^{-09} (pool)	7×10^{-13}	Up
CDK5/p35	2×10^{-10}	NM	Up
CK-MB	1×10^{-08} (pool)	NM	Down
CNDP1	3×10^{-08}	NM	Down
Contactin-5	3×10^{-11}	NM	Down
CSK	3×10^{-10}	5×10^{-13}	Up
CyclophilinA	1×10^{-09} (pool)	2×10^{-13}	Up
Endostatin	5×10^{-10}	1×10^{-13}	Up
ERBB1	1×10^{-10}	4×10^{-14}	Down
FGF-17	5×10^{-10} (pool)	NM	Up
FYN	3×10^{-09} (pool)	NM	Up
GAPDH	8×10^{-12}	4×10^{-13}	Up
HMG-1	2×10^{-10}	1×10^{-12}	Up
HSP 90α	1×10^{-10}	1×10^{-12}	Up
HSP90β	2×10^{-10}	4×10^{-12}	Up
IGFBP-2	6×10^{-10}	9×10^{-13}	Up
IL-15 Rα	4×10^{-11} (pool)	1×10^{-13}	Up
IL-17B	3×10^{-11} (pool)	4×10^{-13}	Up
IMB1	8×10^{-08} (pool)	NM	Up
Kallikrein 7	6×10^{-11}	2×10^{-12}	Down
KPCI	9×10^{-09}	NM	Up
LDH-H1	1×10^{-09}	8×10^{-13}	Up
LGMN	7×10^{-09}	NM	Up
LRIG3	3×10^{-11}	8×10^{-14}	Down
Macrophage mannose receptor	1×10^{-09}	1×10^{-11}	Up
MEK1	6×10^{-10}	NM	Up
METAP1	7×10^{-11}	9×10^{-13}	Up
Midkine	2×10^{-10}	4×10^{-11}	Up
MIP-5	9×10^{-09} (pool)	2×10^{-13}	Up
MK13	2×10^{-09}	NM	Up
MMP-7	7×10^{-11}	3×10^{-13}	Up
NACA	2×10^{-11}	NM	Up
NAGK	2×10^{-09} (pool)	NM	Up

TABLE 37-continued

Aptamer To Designated Biomarker	Solution K_d (M)	Assay LLOQ (M)	Up or Down Regulated
PARC	9×10^{-11}	1×10^{-13}	Up
Proteinase-3	5×10^{-09} (pool)	4×10^{-12}	Up
Prothrombin	5×10^{-09}	1×10^{-12}	Down
PTN	4×10^{-11}	5×10^{-12}	Up
RAC1	7×10^{-11}	NM	Up
Renin	3×10^{-11}	3×10^{-13}	Up
RGM-C	3×10^{-11}	NM	Down
SCF sR	5×10^{-11}	3×10^{-12}	Down

TABLE 37-continued

Aptamer To Designated Biomarker	Solution K_d (M)	Assay LLOQ (M)	Up or Down Regulated
sL-Selectin	2×10^{-10} (pool)	2×10^{-13}	Down
TCTP	2×10^{-11} (pool)	NM	Up
UBE2N	6 × 10−11 (pool)	NM	Up
Ubiquitin + 1	2×10^{-10}	1×10^{-12}	Up
VEGF	4×10^{-10}	9×10^{-14}	Up
YES	2×10^{-09}	NM	Up

TABLE 38

Parameters for Smoker Control Group

Biomarker # from Table 1	Biomarker	μ_c	σ_c^2	μ_d	σ_d^2	KS	p-value	AUC
1	AMPM2	3.05	1.07E−02	3.20	3.62E−02	0.45	5.55E−24	0.75
4	BLC	2.58	1.23E−02	2.72	3.97E−02	0.37	8.72E−17	0.74
5	BMP-1	4.13	1.32E−02	4.00	2.01E−02	0.38	1.21E−17	0.75
6	BTK	3.12	2.44E−01	3.51	2.45E−01	0.35	3.25E−15	0.72
7	C1s	4.01	3.47E−03	4.06	4.23E−03	0.31	4.68E−12	0.69
8	C9	5.31	3.54E−03	5.38	5.37E−03	0.43	3.49E−22	0.75
15	CD30 Ligand	3.21	2.86E−03	3.26	4.42E−03	0.31	1.08E−11	0.70
16	CDK5-p35	2.98	3.48E−03	3.02	4.75E−03	0.25	1.63E−07	0.67
17	CK-MB	3.25	5.18E−02	3.07	4.89E−02	0.33	1.42E−13	0.71
18	CNDP1	3.65	1.97E−02	3.52	3.07E−02	0.36	4.14E−16	0.73
19	Contactin-5	3.66	9.35E−03	3.59	1.33E−02	0.31	1.67E−11	0.68
20	CSK	3.25	6.59E−02	3.54	1.10E−01	0.41	1.33E−20	0.76
21	CyclophilinA	4.42	6.04E−02	4.65	6.80E−02	0.38	2.17E−17	0.73
22	Endostatin	4.61	4.29E−03	4.67	1.07E−02	0.32	1.42E−12	0.69
23	ERBB1	4.17	2.25E−03	4.10	5.18E−03	0.47	9.39E−27	0.78
24	FGF-17	3.08	1.12E−03	3.11	1.31E−03	0.32	1.07E−12	0.71
25	FYN	3.18	6.88E−02	3.24	7.99E−02	0.13	1.53E−02	0.58
26	GAPDH	3.26	7.32E−02	3.51	1.62E−01	0.40	2.02E−19	0.68
28	HSP90a	4.45	1.86E−02	4.61	1.86E−02	0.50	3.09E−30	0.80
30	IGFBP-2	4.30	3.42E−02	4.48	4.17E−02	0.37	5.40E−17	0.74
31	IL-15 Ra	3.03	9.74E−03	3.12	2.10E−02	0.31	7.31E−12	0.69
34	Kallikrein 7	3.52	8.67E−03	3.44	1.21E−02	0.36	2.47E−15	0.70
35	KPCI	2.58	2.92E−03	2.66	1.01E−02	0.40	2.30E−19	0.74
36	LDH-H1	3.60	8.03E−03	3.67	1.45E−02	0.32	3.70E−12	0.68
38	LRIG3	3.55	3.10E−03	3.50	3.60E−03	0.36	1.39E−15	0.72
40	MEK1	2.81	1.54E−03	2.84	2.75E−03	0.28	1.96E−09	0.67
42	Midkine	3.21	3.13E−02	3.24	5.58E−02	0.13	1.90E−02	0.56
43	MIP-5	3.60	3.65E−02	3.77	5.88E−02	0.34	8.40E−14	0.70
48	PARC	4.90	1.94E−02	5.01	2.13E−02	0.34	7.01E−14	0.71
50	Prothrombin	4.68	5.37E−02	4.53	4.31E−02	0.32	1.09E−12	0.68
51	PTN	3.73	7.08E−03	3.80	7.36E−03	0.34	3.97E−14	0.72
52	RAC1	3.85	6.13E−02	4.09	7.31E−02	0.40	4.60E−19	0.72
53	Renin	3.25	2.52E−02	3.39	6.36E−02	0.30	4.23E−11	0.68
55	SCF sR	3.79	1.11E−02	3.68	1.48E−02	0.37	9.90E−17	0.75
56	sL-Selectin	4.46	5.63E−03	4.40	9.30E−03	0.30	6.24E−11	0.69
57	TCTP	4.19	4.69E−02	4.44	7.43E−02	0.43	9.69E−22	0.76
58	UBE2N	4.42	9.30E−02	4.67	9.53E−02	0.34	6.56E−14	0.72
59	Ubiquitin + 1	4.25	1.75E−02	4.34	1.43E−02	0.31	1.55E−11	0.68

TABLE 39

Parameters for benign nodules control group

Biomarker # from Table 1	Biomarker	μ_c	σ_c^2	μ_d	σ_d^2	KS	p-value	AUC
2	ApoA-I	3.83	1.04E−02	3.77	1.56E−02	0.24	1.67E−07	0.65
3	b-ECGF	3.03	1.27E−03	3.06	1.53E−03	0.30	7.50E−12	0.68

TABLE 39-continued

Parameters for benign nodules control group

Biomarker # from Table 1	Biomarker	μ_c	σ_c^2	μ_d	σ_d^2	KS	p-value	AUC
4	BLC	2.60	1.50E−02	2.72	3.97E−02	0.31	1.77E−12	0.70
5	BMP-1	4.11	1.39E−02	4.00	2.01E−02	0.32	2.00E−13	0.72
8	C9	5.31	4.84E−03	5.38	5.37E−03	0.39	9.42E−20	0.75
9	Cadherin E	4.51	5.91E−03	4.43	9.86E−03	0.37	1.93E−17	0.74
10	Cadherin-6	2.91	3.79E−03	2.98	1.12E−02	0.36	1.42E−16	0.72
11	Calpain I	4.37	1.33E−02	4.50	2.32E−02	0.40	7.63E−21	0.75
12	Catalase	4.27	2.09E−02	4.37	1.30E−02	0.34	4.30E−15	0.72
13	CATC	2.80	5.83E−03	2.86	7.63E−03	0.31	8.55E−13	0.69
14	Cathepsin H	4.59	3.24E−03	4.63	7.54E−03	0.30	4.29E−12	0.66
15	CD30 Ligand	3.21	4.19E−03	3.26	4.42E−03	0.26	4.70E−09	0.68
17	CK-MB	3.23	4.47E−02	3.07	4.89E−02	0.32	2.76E−13	0.70
18	CNDP1	3.65	2.03E−02	3.52	3.07E−02	0.35	2.04E−15	0.72
20	CSK	3.25	7.98E−02	3.54	1.10E−01	0.41	2.35E−21	0.76
23	ERBB1	4.17	2.76E−03	4.10	5.18E−03	0.46	1.22E−26	0.77
24	FGF-17	3.08	1.26E−03	3.11	1.31E−03	0.31	9.59E−13	0.71
26	GAPDH	3.22	7.96E−02	3.51	1.62E−01	0.40	7.88E−21	0.69
27	HMG-1	4.01	4.57E−02	4.19	7.55E−02	0.30	1.99E−11	0.70
28	HSP90a	4.43	2.23E−02	4.61	1.86E−02	0.51	1.26E−33	0.81
29	HSP90b	3.06	3.70E−03	3.14	9.67E−03	0.42	2.73E−22	0.75
30	IGFBP-2	4.32	3.57E−02	4.48	4.17E−02	0.35	2.30E−15	0.73
32	IL-17B	2.19	3.73E−03	2.23	4.16E−03	0.28	3.65E−10	0.68
33	IMB1	3.47	2.21E−02	3.67	5.45E−02	0.42	2.04E−22	0.75
35	KPCI	2.57	3.26E−03	2.66	1.01E−02	0.43	3.57E−23	0.75
37	LGMN	3.13	2.03E−03	3.17	4.15E−03	0.30	1.15E−11	0.69
38	LRIG3	3.55	3.59E−03	3.50	3.60E−03	0.33	9.00E−14	0.71
39	Macrophage mannose receptor	4.10	1.51E−02	4.22	2.48E−02	0.36	7.24E−17	0.72
40	MEK1	2.81	1.77E−03	2.84	2.75E−03	0.31	3.79E−12	0.69
41	METAP1	2.67	2.45E−02	2.89	5.83E−02	0.44	2.99E−24	0.75
44	MK13	2.79	3.38E−03	2.85	4.88E−03	0.36	6.16E−17	0.74
45	MMP-7	3.64	3.24E−02	3.82	4.85E−02	0.37	1.89E−17	0.73
46	NACA	3.11	8.28E−03	3.21	2.63E−02	0.34	4.91E−15	0.70
47	NAGK	3.71	2.04E−02	3.84	2.63E−02	0.38	7.50E−19	0.73
49	Proteinase-3	3.95	9.09E−02	4.18	1.23E−01	0.30	2.22E−11	0.69
50	Prothrombin	4.67	4.19E−02	4.53	4.31E−02	0.32	2.17E−13	0.68
54	RGM-C	4.44	4.85E−03	4.38	6.13E−03	0.30	1.00E−11	0.69
55	SCF sR	3.77	9.71E−03	3.68	1.48E−02	0.35	1.96E−15	0.72
60	VEGF	3.55	8.80E−03	3.62	1.14E−02	0.30	1.27E−11	0.69
61	YES	2.97	9.54E−04	3.00	1.73E−03	0.29	7.59E−11	0.67

TABLE 40

Sensitivity + Specificity for Exemplary Combinations of Biomarkers

#										Sensitivity	Specificity	Sensitivity + Specificity	AUC
1	SCFsR									0.629	0.727	1.356	0.75
2	SCFsR	HSP90a								0.761	0.753	1.514	0.84
3	SCFsR	HSP90a	ERBB1							0.775	0.827	1.602	0.87
4	SCFsR	HSP90a	ERBB1	PTN						0.784	0.861	1.645	0.89
5	SCFsR	HSP90a	ERBB1	PTN	BTK					0.84	0.844	1.684	0.9
6	SCFsR	HSP90a	ERBB1	PTN	BTK	CD30 Ligand				0.822	0.869	1.691	0.9
7	SCFsR	HSP90a	ERBB1	PTN	BTK	CD30 Ligand	Kallikrein7			0.845	0.875	1.72	0.91
8	SCFsR	HSP90a	ERBB1	PTN	BTK	CD30 Ligand	Kallikrein7	LRIG3		0.859	0.864	1.723	0.91
9	SCFsR	HSP90a	ERBB1	PTN	BTK	CD30 Ligand	Kallikrein7	LRIG3	LDH-H1	0.869	0.872	1.741	0.91
10	SCFsR	HSP90a	ERBB1	PTN	BTK	CD30 Ligand	Kallikrein7	LRIG3	LDH-H1	PARC	0.873	0.878	1.751	0.91

TABLE 41

Parameters derived from training set for naïve Bayes classifier.

Biomarker	μ_c	σ_c^2	μ_d	σ_d^2
HSP90b	3.06	3.70E−03	3.14	9.67E−03
ERBB1	4.17	2.76E−03	4.10	5.18E−03
RGM-C	4.44	4.85E−03	4.38	6.13E−03
CadherinE	4.51	5.91E−03	4.43	9.86E−03
SCFsR	3.77	9.71E−03	3.68	1.48E−02
METAP1	2.67	2.45E−02	2.89	5.83E−02
b-ECGF	3.03	1.27E−03	3.06	1.53E−03
CK-MB	3.23	4.47E−02	3.07	4.89E−02
ART	2.93	1.92E−03	2.97	2.98E−03
HSP90a	4.43	2.23E−02	4.61	1.86E−02

TABLE 42

Calculation details for naïve Bayes classifier

Biomarker	Log (RFU)	$-\frac{1}{2}\left(\frac{x_i-\mu_{c,i}}{\sigma_{c,i}}\right)^2$	$-\frac{1}{2}\left(\frac{x_i-\mu_{d,i}}{\sigma_{d,i}}\right)^2$	$\ln\frac{\sigma_{d,i}}{\sigma_{c,i}}$	Ln (likelihood)	likelihood
HSP90b	3.133	−0.797	−0.002	0.480	−0.315	0.730
ERBB1	4.127	−0.374	−0.050	0.315	−0.009	0.991
RGM-C	4.476	−0.175	−0.727	0.117	0.669	1.952
Cadherin E	4.575	−0.358	−1.071	0.256	0.969	2.636
SCFsR	3.783	−0.007	−0.362	0.209	0.565	1.759
METAP1	2.548	−0.318	−0.975	0.434	1.091	2.977
b-ECGF	3.022	−0.037	−0.389	0.096	0.448	1.565
CK-MB	3.494	−0.754	−1.823	0.044	1.113	3.044
ART	2.918	−0.041	−0.401	0.218	0.578	1.783
HSP90a	4.444	−0.004	−0.757	−0.090	0.664	1.942

What is claimed is:

1. A method for detecting protein levels of a set of proteins in a human, the method comprising:

contacting a biological sample from the human with a set of capture reagents, wherein the biological sample is selected from the group consisting of whole blood, plasma, serum and urine, further wherein the capture reagents are aptamers comprising a 5-position pyrimidine modification, further wherein the 5-position pyrimidine modification comprises a substitution with a hydrophobic chemical group selected from the group consisting of benzyl, indole and napthyl, further wherein each capture reagent specifically binds to a different protein of the set of proteins comprising at least C9, MMP-7, ERBB1, IGFBP2, SCFsR and CNDP1; and measuring the level of each protein of the set of proteins based on measurement of the capture reagents.

2. The method of claim **1**, wherein measurement of the protein levels comprises performing an in vitro assay.

3. The method of claim **1**, wherein the biological sample is serum.

4. The method of claim **1**, wherein the human is a smoker.

5. The method of claim **4**, wherein the set of proteins, in addition to C9, MMP-7, ERBB1, IGFBP2, SCFsR and CNDP1, comprises one or more proteins selected from the group consisting of AMPM2; BLC; BMP-1; BTK; Cls; CD30 Ligand; CDK5-p35; CK-MB; Contactin-5; CSK; Cyclophilin A; Endostatin; FGF-17; FYN; GAPDH, liver; HSP 90a; IL-15 Ra; Kallikrein 7; KPCI; LDH-H 1; LRIG3; MEK1; Midkine; MIP-5; PARC; Prothrombin; PTN; RAC1; Renin; sL-Selectin; SELL; TCTP; UBE2N; and Ubiquitin+1.

6. The method of claim **1**, wherein the human has a pulmonary nodule.

7. The method of claim **6**, wherein the set of proteins, in addition to C9, MMP-7, ERBB1, IGFBP2, SCFsR and CNDP1, comprises one or more proteins selected from the group consisting of Apo A-I; b-ECGF; BLC; BMP-1; Cadherin E; Cadherin-6; Calpain I; Catalase; CATC; Cathepsin H; CD30 Ligand; CK-MB; CSK; FGF-17; GAPDH, liver; HMG-1; HSP 90a; HSP 90b; IL-17B; IMB1; KPCI; LGMN; LRIG3; Macrophage mannose receptor; MEK1; METAP1; MK13; NACA; NAGK; Proteinase-3; Prothrombin; RGM-C; SELL; VEGF; and YES.

8. The method of claim **1**, wherein the protein biomarkers, in addition to C9, MMP-7, ERBB1, IGFBP2, SCFsR and CNDP1, comprise LRIG3 and SELL.

9. The method of claim **1**, further comprising measuring the level of the protein PSA-ACT.

* * * * *